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=> fil reg
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

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STRUCTURE FILE UPDATES:     8 JUL 2003  HIGHEST RN 544651-49-2
DICTIONARY FILE UPDATES:    8 JUL 2003  HIGHEST RN 544651-49-2

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> e tissue ischemia/cn 5
E1            1     TISSUE INHIBITOR OF METALLOPROTEINASES-3 (MOUSE PCC4 TERATOC
                    ARCINOMA CELL CLONE 4 GENE TIMP-3 PRECURSOR)/CN
E2            1     TISSUE INHIBITOR OF METALLOPROTEINASES-3 (XENOPUS LAEVIS PRE
                    CURSOR REDUCED)/CN
E3            0 --> TISSUE ISCHEMIA/CN
E4            1     TISSUE KALLIKREIN/CN
E5            1     TISSUE KALLIKREIN (CATTLE GENE KLK1 FRAGMENT)/CN

=> e ischemia/cn 5
E1            1     ISCEON 59/CN
E2            1     ISCHELIUM/CN
E3            0 --> ISCHEMIA/CN
E4            1     ISCHEMIA RESPONSIVE 94 KDA PROTEIN (RATTUS NORVEGICUS STRAIN
                     SD GENE IRP94)/CN
E5            1     ISCHEMIA RESPONSIVE 94 KILODALTON PROTEIN (RAT STRAIN SD HIP
                    POCAMPUS GENE IRP94)/CN

=> e
E6            1     ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE
                    QID-1001 FRAGMENT)/CN
E7            1     ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE
                    QID-1003 FRAGMENT)/CN
E8            1     ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE
                    QID-1005 FRAGMENT)/CN
E9            1     ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE
                    QID-1007 FRAGMENT)/CN
E10           1     ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE
                    QID-1014 FRAGMENT)/CN
E11           1     ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE
                    QID-1018 FRAGMENT)/CN
E12           1     ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE

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                  QID-1022 FRAGMENT)/CN
E13          1    ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE
                  QID-1024 FRAGMENT)/CN
E14          1    ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE
                  QID-1026 FRAGMENT)/CN
E15          1    ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE
                  QID-1029 FRAGMENT)/CN
E16          1    ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE
                  QID-1034 FRAGMENT)/CN
E17          1    ISCHEMIA-ASSOCIATED PROTEIN (MUS MUSCULUS CLONE WO0188188-SE
                  QID-1036 FRAGMENT)/CN

=> s ischemia?/cn
L1          355 ISCHEMIA?/CN

=> e beta tocopherol/cn 5
E1           1    BETA SUBUNIT OF MALONATE DECARBOXYLASE (XANTHOMONAS AXONOPOD
                  IS CITRI STRAIN 306 GENE MDCB)/CN
E2           1    BETA SUBUNIT OF MALONATE DECARBOXYLASE (XANTHOMONAS CAMPESTR
                  IS CAMPESTRIS STRAIN ATCC33913 GENE MDCB)/CN
E3           0 --> BETA TOCOPHEROL/CN
E4           1    BETA TOXIN (CLOSTRIDIUM PERFRINGENS TYPE C STRAIN INDIAN CLO
                  NE PCPB MATURE FORM)/CN
E5           1    BETA TRANSDUCIN-LIKE PROTEIN (STREPTOMYCES AVERMITILIS STRAI
                  N MA-4680)/CN

=> e "beta-tocopherol"/cn 5
E1           1    BETA-THROMBOGLOBULIN-LIKE PROTEIN (HUMAN)/CN
E2           1    BETA-TIMELETS/CN
E3           0 --> BETA-TOCOPHEROL/CN
E4           1    BETA-TONOPLAST INTRINSIC PROTEIN (ORYZA SATIVA JAPONICA GENE
                   OSJNBA0051D19.19)/CN
E5           1    BETA-TRANSDUCIN REPEAT CONTAINING (HUMAN CLONE MGC:40028 IMA
                  GE:5180993)/CN

=> e "delta-tocopherol"/cn 5
E1           1    DELTA-SEAL/CN
E2           1    DELTA-STAB/CN
E3           0 --> DELTA-TOCOPHEROL/CN
E4           1    DELTA-TONE 9000/CN
E5           1    DELTA-V (ERYTHROVIRUS B19 CLONE F-2 N-TERMINAL FRAGMENT)/CN

=> e "gamma-tocopherol"/cn 5
E1           1    GAMMA-SARCOGLYCAN (CANIS FAMILIARIS CLONE 405 H01 GENE SGCG)
                  /CN
E2           1    GAMMA-TAB/CN
E3           0 --> GAMMA-TOCOPHEROL/CN
E4           1    GAMMA-TOCOPHEROL METHYLTRANSFERASE (ARABIDOPSIS THALIANA CLO
                  NE F13O11 GENE F13O11.27)/CN
E5           1    GAMMA-TOCOPHEROL METHYLTRANSFERASE (NOSTOC SP. PCC 7120 GENE
                   ALR1803)/CN

=> e ".gamma.-tocopherol"/cn 5
E1           1    .GAMMA.-TOCOMONOENOL/CN
E2           1    .GAMMA.-TOCOPHERAMINE/CN
E3           1 --> .GAMMA.-TOCOPHEROL/CN
E4           1    .GAMMA.-TOCOPHEROL ACETATE/CN
E5           1    .GAMMA.-TOCOPHEROL ALLOPHANATE/CN

=> s e3;e ".delta.-tocopherol"/cn 5


Searched by: Mary Hale 308-4258 CM-1 1E01
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L2            1 .GAMMA.-TOCOPHEROL/CN


E1            1      .DELTA.-TOCOMONOENOL/CN
E2            1      .DELTA.-TOCOPHERAMINE/CN
E3            1 --> .DELTA.-TOCOPHEROL/CN
E4            1      .DELTA.-TOCOPHEROL ACETATE/CN
E5            1      .DELTA.-TOCOPHEROL DICHLOROPHOSPHATE/CN

=> s e3;e ".beta.-tocopherol"/cn 5
L3            1 .DELTA.-TOCOPHEROL/CN


E1            1      .BETA.-TOCOMONOENOL/CN
E2            1      .BETA.-TOCOPHERAMINE/CN
E3            1 --> .BETA.-TOCOPHEROL/CN
E4            1      .BETA.-TOCOPHEROL ACETATE/CN
E5            1      .BETA.-TOCOPHEROL ALLOPHANATE/CN

=> s e3
L4            1 .BETA.-TOCOPHEROL/CN

=> e metabolites/cn 5
E1            1      METABOLITE-PROTON SYMPORTER (BRUCELLA MELITENSIS BIOVAR SUIS
                      STRAIN 1330 GENE BR1453)/CN
E2            1      METABOLITE-PROTON SYMPORTER (PSEUDOMONAS PUTIDA STRAIN KT244
                      0 GENE PP1458)/CN
E3            0 --> METABOLITES/CN
E4            1      METABOND/CN
E5            2      METABORATE/CN

=> e metabolite/cn 5
E1            1      METABOLISM FLAVOPROTEIN (YERSINIA PESTIS STRAIN CO92 GENE DF
                      P)/CN
E2            1      METABOLIT/CN
E3            0 --> METABOLITE/CN
E4            1      METABOLITE A-27106/CN
E5            1      METABOLITE C/CN

=> s metabolite?/cn
L5           49 METABOLITE?/CN

=> s (chromans or chroman or benzopyran or benzopyrans or flavones or flavone or
flavonoid or chrysin or dihyroxyflavone or daidzein or dihydroxyisoflavone or
hesperetin)/cn
              0 CHROMANS/CN
              1 CHROMAN/CN
              1 BENZOPYRAN/CN
              0 BENZOPYRANS/CN
              0 FLAVONES/CN
              1 FLAVONE/CN
              0 FLAVONOID/CN
              1 CHRYSIN/CN
              0 DIHYROXYFLAVONE/CN
              1 DAIDZEIN/CN
              0 DIHYDROXYISOFLAVONE/CN
              1 HESPERETIN/CN
L6            6 (CHROMANS OR CHROMAN OR BENZOPYRAN OR BENZOPYRANS OR FLAVONES
                OR FLAVONE OR FLAVONOID OR CHRYSIN OR DIHYROXYFLAVONE OR DAIDZEI
                N OR DIHYDROXYISOFLAVONE OR HESPERETIN)/CN


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=> s (luteolin or tetrahydroxyflavone or flacitran or quercetin or bioflavonoids or
bromoquercetin or rutin or biochanin)/cn
             1 LUTEOLIN/CN
             0 TETRAHYDROXYFLAVONE/CN
             1 FLACITRAN/CN
             1 QUERCETIN/CN
             0 BIOFLAVONOIDS/CN
             0 BROMOQUERCETIN/CN
             1 RUTIN/CN
             1 BIOCHANIN/CN
L7           4 (LUTEOLIN OR TETRAHYDROXYFLAVONE OR FLACITRAN OR QUERCETIN OR
               BIOFLAVONOIDS OR BROMOQUERCETIN OR RUTIN OR BIOCHANIN)/CN

=> fil medl,caplus,biosis,embase,jicst,wpids
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   109.10     109.31

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=> s (l1 or ischemi? or localiz? anemia or blood deficienc?(5a)(organ or tissue))
L8       148634 FILE MEDLINE
L9        61281 FILE CAPLUS
L10      159684 FILE BIOSIS
L11      170947 FILE EMBASE
L12       27745 FILE JICST-EPLUS
L13        7523 FILE WPIDS

TOTAL FOR ALL FILES
L14      575814 (L1 OR ISCHEMI? OR LOCALIZ? ANEMIA OR BLOOD DEFICIENC?(5A)(ORGAN
                OR TISSUE))

=> s l14 and (vitamin e or l2 or l3 or l4 or (beta or delta or gamma)(W)tocopherol
or l5 or l6 or l7 or metabolites or chroman? or benzopyran? or ?flavonoid? or
?flavone? or chrysin? or dihydroxyflavone)
L15        2860 FILE MEDLINE
L16        2458 FILE CAPLUS
L17        2374 FILE BIOSIS
L18        2819 FILE EMBASE
LEFT TRUNCATION IGNORED FOR '?FLAVONOID?' FOR FILE 'JICST-EPLUS'
LEFT TRUNCATION IGNORED FOR '?FLAVONE?' FOR FILE 'JICST-EPLUS'
L19         327 FILE JICST-EPLUS


Searched by: Mary Hale 308-4258 CM-1 1E01
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L20         227 FILE WPIDS

TOTAL FOR ALL FILES
L21       11065 L14 AND (VITAMIN E OR L2 OR L3 OR L4 OR (BETA OR DELTA OR GAMMA)
                (W)TOCOPHEROL OR L5 OR L6 OR L7 OR METABOLITES OR CHROMAN? OR
                BENZOPYRAN? OR ?FLAVONOID? OR ?FLAVONE? OR CHRYSIN? OR DIHYDROXY
                FLAVONE)
Left truncation is not valid in the specified search field in the
specified file.  The term has been searched without left truncation.
Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID'
would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you
used a truncation symbol after a punctuation mark, the system may
interpret the truncation symbol as being at the beginning of a term.
Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> s l14 and (daidzein or hesperetin or luteolin or tetrahydroxyflavone or
flacitran or quercetin or bioflavonoids or bromoquercetin or rutin or biochanin)
L22         141 FILE MEDLINE
L23         113 FILE CAPLUS
L24          90 FILE BIOSIS
L25         157 FILE EMBASE
L26           4 FILE JICST-EPLUS
L27          16 FILE WPIDS

TOTAL FOR ALL FILES
L28         521 L14 AND (DAIDZEIN OR HESPERETIN OR LUTEOLIN OR TETRAHYDROXYFLAVO
                NE OR FLACITRAN OR QUERCETIN OR BIOFLAVONOIDS OR BROMOQUERCETIN
                OR RUTIN OR BIOCHANIN)

=> s (l21 or l28) and (treat? or therap? or prophylaxis or prevent?)
L29        1529 FILE MEDLINE
L30        1122 FILE CAPLUS
L31         924 FILE BIOSIS
L32        1473 FILE EMBASE
L33         142 FILE JICST-EPLUS
L34         228 FILE WPIDS

TOTAL FOR ALL FILES
L35        5418 (L21 OR L28) AND (TREAT? OR THERAP? OR PROPHYLAXIS OR PREVENT?)

=> s (l1 or ischemia)(10a)tissue and (treat? or therap? or prophylaxis or prevent?)
L36        1484 FILE MEDLINE
L37        1266 FILE CAPLUS
L38        1305 FILE BIOSIS
L39        1581 FILE EMBASE
L40         120 FILE JICST-EPLUS
L41         316 FILE WPIDS

TOTAL FOR ALL FILES
L42        6072 (L1 OR ISCHEMIA)(10A) TISSUE AND (TREAT? OR THERAP? OR PROPHYLAX
                IS OR PREVENT?)

=> s l42 and (daidzein or hesperetin or luteolin or tetrahydroxyflavone or
flacitran or quercetin or bioflavonoids or bromoquercetin or rutin or biochanin)
L43           3 FILE MEDLINE
L44           6 FILE CAPLUS
L45           1 FILE BIOSIS


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L46           3 FILE EMBASE
L47           0 FILE JICST-EPLUS
L48           1 FILE WPIDS

TOTAL FOR ALL FILES
L49          14 L42 AND (DAIDZEIN OR HESPERETIN OR LUTEOLIN OR TETRAHYDROXYFLAVO
                NE OR FLACITRAN OR QUERCETIN OR BIOFLAVONOIDS OR BROMOQUERCETIN
                OR RUTIN OR BIOCHANIN)

=> s l42 and (vitamin e or l2 or l3 or l4 or (beta or delta or gamma)(W)tocopherol
or l5 or l6 or l7 or metabolites or chroman? or benzopyran? or ?flavonoid? or
?flavone? or chrysin? or dihydroxyflavone)
L50          91 FILE MEDLINE
L51          75 FILE CAPLUS
L52          63 FILE BIOSIS
L53          84 FILE EMBASE
LEFT TRUNCATION IGNORED FOR '?FLAVONOID?' FOR FILE 'JICST-EPLUS'
LEFT TRUNCATION IGNORED FOR '?FLAVONE?' FOR FILE 'JICST-EPLUS'
L54          10 FILE JICST-EPLUS
L55          14 FILE WPIDS

TOTAL FOR ALL FILES
L56         337 L42 AND (VITAMIN E OR L2 OR L3 OR L4 OR (BETA OR DELTA OR GAMMA)
                (W)TOCOPHEROL OR L5 OR L6 OR L7 OR METABOLITES OR CHROMAN? OR
                BENZOPYRAN? OR ?FLAVONOID? OR ?FLAVONE? OR CHRYSIN? OR DIHYDROXY
                FLAVONE)
Left truncation is not valid in the specified search field in the
specified file.  The term has been searched without left truncation.
Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID'
would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you
used a truncation symbol after a punctuation mark, the system may
interpret the truncation symbol as being at the beginning of a term.
Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> s (l1 or ischemia)(3a)tissue and (treat? or therap? or prophylaxis or prevent?)
L57         706 FILE MEDLINE
L58         644 FILE CAPLUS
L59         580 FILE BIOSIS
L60         703 FILE EMBASE
L61          53 FILE JICST-EPLUS
L62         178 FILE WPIDS

TOTAL FOR ALL FILES
L63        2864 (L1 OR ISCHEMIA)(3A) TISSUE AND (TREAT? OR THERAP? OR PROPHYLAXI
                S OR PREVENT?)

=> s l63 and (vitamin e or l2 or l3 or l4 or (beta or delta or gamma)(W)tocopherol
or l5 or l6 or l7 or metabolites or chroman? or benzopyran? or ?flavonoid? or
?flavone? or chrysin? or dihydroxyflavone)
L64          40 FILE MEDLINE
L65          38 FILE CAPLUS
L66          23 FILE BIOSIS
L67          30 FILE EMBASE
LEFT TRUNCATION IGNORED FOR '?FLAVONOID?' FOR FILE 'JICST-EPLUS'
LEFT TRUNCATION IGNORED FOR '?FLAVONE?' FOR FILE 'JICST-EPLUS'
L68           5 FILE JICST-EPLUS
L69          10 FILE WPIDS


Searched by: Mary Hale 308-4258 CM-1 1E01
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TOTAL FOR ALL FILES
L70 146 L63 AND (VITAMIN E OR L2 OR L3 OR L4 OR (BETA OR DELTA OR GAMMA) (W)TOCOPHEROL OR L5 OR L6 OR L7 OR METABOLITES OR CHROMAN? OR BENZOPYRAN? OR ?FLAVONOID? OR ?FLAVONE? OR CHRYSIN? OR DIHYDROXY FLAVONE)
Left truncation is not valid in the specified search field in the specified file. The term has been searched without left truncation. Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID' would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you used a truncation symbol after a punctuation mark, the system may interpret the truncation symbol as being at the beginning of a term. Implied proximity is used in search fields indexed as single words, for example, the Basic Index.

=> s l63 and (daidzein or hesperetin or luteolin or tetrahydroxyflavone or flacitran or quercetin or bioflavonoids or bromoquercetin or rutin or biochanin)
L71 1 FILE MEDLINE
L72 6 FILE CAPLUS
L73 1 FILE BIOSIS
L74 1 FILE EMBASE
L75 0 FILE JICST-EPLUS
L76 1 FILE WPIDS

TOTAL FOR ALL FILES
L77 10 L63 AND (DAIDZEIN OR HESPERETIN OR LUTEOLIN OR TETRAHYDROXYFLAVONE OR FLACITRAN OR QUERCETIN OR BIOFLAVONOIDS OR BROMOQUERCETIN OR RUTIN OR BIOCHANIN)

=> s l70 or l77
L78 40 FILE MEDLINE
L79 38 FILE CAPLUS
L80 23 FILE BIOSIS
L81 30 FILE EMBASE
L82 5 FILE JICST-EPLUS
L83 10 FILE WPIDS

TOTAL FOR ALL FILES
L84 146 L70 OR L77

=> dup rem l84
PROCESSING COMPLETED FOR L84
L85 93 DUP REM L84 (53 DUPLICATES REMOVED)

=> d 1-93 cbib abs;dis his l63-

L85 ANSWER 1 OF 93 CAPLUS COPYRIGHT 2003 ACS
2003:356245 Document No. 138:348735 Use of an Opuntia ficus-indica extract and compounds isolated therefrom for protecting nerve cells. Lee, Yong Sup; Park, Hokoon; Jin, Changbae; Kim, Hyoung Ja; Cho, Jungsook; Park, Mijeong; Song, Yunseon (Korea Institute of Science and Technology, S. Korea). PCT Int. Appl. WO 2003037324 A1 20030508, 42 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG,

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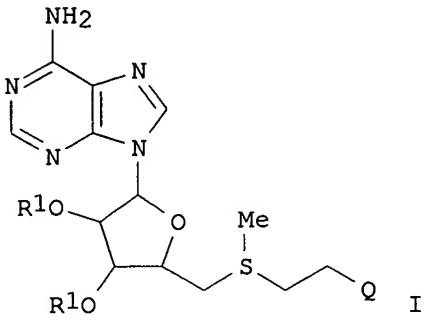
CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-KR2010 20021029. PRIORITY: KR 2001-66810 20011029.

AB The invention discloses the use of an Et acetate ext. of Opuntia ficus-indica and compds. isolated therefrom for **preventing** and **treating** brain diseases, e.g. Alzheimer's disease, stroke, and Parkinson's disease; cell and **tissue** damage caused by **ischemia**; or cardiovascular system disease, e.g. myocardial infarction.

L85 ANSWER 2 OF 93 CAPLUS COPYRIGHT 2003 ACS

2003:319452 Document No. 138:314630 Orthomolecular sulfo-adenosylmethionine derivatives with antioxidant properties. Wilburn, Michael D. (USA). U.S. Pat. Appl. Publ. US 2003078231 A1 20030424, 17 pp. (English). CODEN: USXXCO. APPLICATION: US 2001-886612 20010622.

GI



I

AB Disclosed are orthomol. sulfo-adenosylmethionine deriv. compds., compns., and their uses for effecting a biol. activity in an animal, such as neurochem. activity; liver biol. activity; heart and artery function; cartilage, bone and joint health; stomach and/or intestinal lining resistance to ulceration; immune function; cell membrane integrity; and pain and inflammation. The compds. of the present invention are further useful for **preventing** or **treating** diseases or conditions; **treating** viral infections, infectious diseases, leukemia, and obesity; and reducing the risk of Sudden Infant Death Syndrome in an animal. The compds. of the present invention are I (R1 = H, C1-C10 alkyl, C2-C10 alkenyl or alkynyl, -C(O)R2; R2 = C1-C10 alkyl, C2-C10 alkenyl or alkynyl; Q = -C(NH3)C(O)AX, -C(COOH)NHX; A = O, N; X = a defined reaction product) or pharmaceutically acceptable salt, ester or solvate thereof. .alpha.-(S-adenosylmethionine)-O-tocopherol was prepd. from N-Acetyl-S-benzyl-L-homocysteine, .alpha.-tocopherol, and 5'-O-p-Tolylsulfonyladenosine.

L85 ANSWER 3 OF 93 MEDLINE

2003204276 Document Number: 22610044. PubMed ID: 12626438. Hypoxia causes down-regulation of 11 beta-hydroxysteroid dehydrogenase type 2 by induction of Egr-1. Heiniger Christian D; Kostadinova Radina M; Rochat Mascha K; Serra Andreas; Ferrari Paolo; Dick Bernhard; Frey Brigitte M; Frey Felix J. (Division of Nephrology and Hypertension, University of Berne, 3010 Bërne, Switzerland.) FASEB JOURNAL, (2003 May) 17 (8) 917-9. Journal code: 8804484. ISSN: 1530-6860. Pub. country: United States. Language: English.

Searched by: Mary Hale 308-4258 CM-1 1E01

AB Hypoxia causes several renal tubular dysfunctions, including abnormal handling of potassium and sodium and increased blood pressure. Therefore, we investigated the impact of hypoxia on 11beta-hydroxysteroid dehydrogenase (11beta-HSD2) enzyme, a crucial prereceptor gatekeeper for renal glucocorticosteroid-mediated mineralocorticoid action. The effect of hypoxia was assessed in vitro by incubating LLC-PK1 cells with antimycin A, an inhibitor of mitochondrial oxidative phosphorylation. Antimycin A induced a dose- and time-dependent reduction of 11beta-HSD2 activity. The early growth response gene, Egr-1, a gene known to be stimulated by hypoxia was investigated because of a potential Egr-1 binding site in the promoter region of 11beta-HSD2. Antimycin A induced Egr-1 protein and Egr-1-regulated luciferase gene expression. This induction was **prevented** with the MAPKK inhibitor PD 98059. Overexpression of Egr-1 reduced endogenous 11beta-HSD2 activity in LLC-PK1 cells, indicating that MAPK ERK is involved in the regulation of 11beta-HSD2 in vitro. In vivo experiments in rats revealed that Egr-1 protein increases, whereas 11beta-HSD2 mRNA decreases, in kidney **tissue** after unilateral renal **ischemia** and in humans the renal activity of 11beta-HSD2 as assessed by the urinary ratio of (tetrahydrocortisol+5alpha-tetrahydrocortisol)/tetrahydrocortisone declined when volunteers were exposed to hypoxemia at high altitude up to 7000 m. Thus, hypoxia decreases 11beta-HSD2 transcription and activity by inducing Egr-1 in vivo and in vitro. This mechanism might account for enhanced renal sodium retention and hypertension associated with hypoxic conditions.

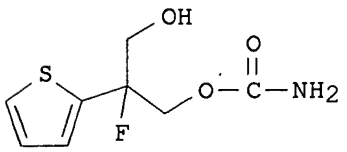
L85 ANSWER 4 OF 93 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
2002:465811 Document No. 137:28330 Compositions and methods for the **treatment** of **tissue ischemia**. Miller, Guy Michael; Brown, Lesley A.; Del Balzo, Ughetta; Flaim, Stephen; Boddupalli, Sekhar; Wang, Bing (Galileo Laboratories, Inc., USA). PCT Int. Appl. WO 2002047680 A2 20020620, 130 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US50984 20011214. PRIORITY: US 2000-PV256269 20001215; US 2001-PV296581 20010606; US 2001-PV296580 20010606; US 2001-PV343575 20011019.

AB The present invention provides compns. and methods for the **treatment** of **tissue ischemia**, and in particular, cerebral ischemia. In particular, the present invention provides gamma-, beta-, or **delta-tocopherol** enriched tocopherol compns. and gamma-, beta, or **delta-tocopherol** metabolite enriched compns. and/or **flavonoid** enriched and/or a **flavonoid** deriv. enriched compns. and methods for their use in **preventing** or **treating** a tissue ischemic condition or a cerebral ischemic condition. The present invention also provides pharmaceutical compns. comprising gamma-, beta-, or **delta-tocopherol** enriched tocopherol compn., a gamma-, beta-, or **delta-tocopherol** metabolite enriched compns. or **flavonoid** enriched compns. or **flavonoid** deriv. enriched compns.

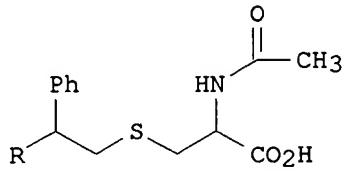
L85 ANSWER 5 OF 93 CAPLUS COPYRIGHT 2003 ACS
2002:555302 Document No. 137:109129 Preparation of 2-aryl-1,3-propanediol carbamates as felbamate analogs. MacDonald, Timothy L. (University of

Virginia Patent Foundation, USA). PCT Int. Appl. WO 2002056827 A2 20020725, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US47665 20011023. PRIORITY: US 2000-PV243023 20001025; US 2000-PV243024 20001025.

GI



II



III

AB Title compds. R1R2C(CH2R3)CH2OCONH2 [R2 = F, Cl; R3 = OH, OCONH2; R1 = alkyl, cycloalkyl, thiophenyl, pyridinyl, pyrimidinyl, etc.; I] were prepd. Di-Et 2-(2-thienyl)malonate was converted to the .alpha.-fluoro deriv. (THF, NaH, Selectfluor) the product reduced to the diol, converted to the bis(carbamate) and finally to II (THF, NaH, TBSCl, 60 min; CDI, cooled to -78.degree., NH3). Addnl., a method was disclosed to det. levels of atropaldehyde-derived **metabolites** III [R = COOH, CH2OH]. I are felbamate derivs. modified to **prevent** the formation of **metabolites** that are believed to be responsible for the toxicity assocd. with felbamate **therapy**. I are useful in the **treatment** of neurol. diseases such as epilepsy and neuropathic pain, and to **treat** tissue damage resulting form ischemic events.

L85 ANSWER 6 OF 93 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-599694 [64] WPIDS
AB WO 200257211 A UPAB: 20021007
NOVELTY - Symmetrically disubstituted aromatic compounds (I)-(VIII) are new.

DETAILED DESCRIPTION - Symmetrically disubstituted aromatic compounds of formula (I)-(VIII) or its prodrugs, **metabolites** or salts are new.

A = CH2, O or S;

n = 0-4;

Y = H, optionally substituted cycloalkyl, aryl or heteroaryl, or NR1R2;

R1, R2, R4 = H or optionally substituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino or arylamino; or

R1+R2 = optionally substituted 5-7 membered heterocyclic ring containing 1-3 O, N or S;

X = C=O, CH2 or CCl2;

Z = optionally substituted heteroaryl, or NR3R4;

R3 = optionally substituted aryl or heteroaryl; or

R3+R4 = optionally substituted 5-6 membered aromatic ring;

Y1 = H, optionally substituted cycloalkyl, aryl or heteroaryl or NR1R2;

Q = optionally substituted aryl or heteroaryl;

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m = 1-3;
R5 = H; and
R6 = optionally substituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino or arylamino; or
R5+R6 = optionally substituted 5-7 membered heterocyclic ring containing 1-3 O, N or S.

INDEPENDENT CLAIMS are also included for:
(1) a pharmaceutical composition comprising (I) and a carrier; and
(2) a method of **treating** or **preventing** diseases or conditions resulting from cell damage or death involving administering (II) or (V) or their prodrugs, **metabolites** or salts.

ACTIVITY - Analgesic; Antiarthritic; Antiarteriosclerotic; Vulnerary; Antidiabetic; Neuroprotective; Nephrotropic; Opthalmological; Dermatological; Immunomodulator; Cardiant; Vasotropic; Osteopathic; Hemostatic; Antibacterial; Immunosuppressive; Cerebroprotective.

MECHANISM OF ACTION - Poly(ADP-ribose)glycohydrolase (PARG) modulator; PARG inhibitor.

9,9-Dichloro-9H-fluorene-2,7-dicarboxylic acid bis-benzyl ester (Ia) was dissolved in dimethylsulfoxide (DMSO). Poly(ADP-ribose)glycohydrolase (PARG) enzyme (0.05 micro l/ml) was added to microtiter plates containing 3H-labeled poly-(ADP-ribose) (10 micro M) in phosphate buffer (50 mM) and B-mercaptoethanol (5 mM). The reaction was incubated at 23 deg. C for 10 minutes and was stopped with the addition of TCA (10 %). 9,9-Dichloro-9H-fluorene-2,7-dicarboxylic acid bis-benzyl ester (Ia) inhibited PARG enzyme with an IC50 of 13.5 micro M.

USE - For modulating or inhibiting poly(ADP-ribose)glycohydrolase (PARG) to **treat** e.g. acute pain, arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma, hyperglycemia, immune senescence, inflammatory bowel disorders, ischemia, macular degeneration, muscular dystrophy, **tissue** damage resulting from **ischemia** and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain, nervous insult, osteoarthritis, osteoporosis, peripheral nerve injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia, septic shock, skin aging, vascular stroke, diseases or disorders relating to lifespan or proliferative capacity of cells and diseases or disease conditions induced or exacerbated by cellular senescence (all claimed).

ADVANTAGE - The compounds are small, easily diffusible and relatively stable.

Dwg.0/0

L85 ANSWER 7 OF 93 CAPLUS COPYRIGHT 2003 ACS

2002:118769 Document No. 137:31062 Mitochondrial contributions to tissue damage in stroke. Sims, Neil R.; Anderson, Michelle F. (Flinders Medical Research Institute, Center for Neuroscience, Department of Medical Biochemistry, Flinders University, School of Medicine, Adelaide, 5001, Australia). Neurochemistry International, 40(6), 511-526 (English) 2002. CODEN: NEUIDS. ISSN: 0197-0186. Publisher: Elsevier Science Ltd..

AB A review. Tissue infarction, involving death of essentially all cells within a part of the brain, is a common pathol. resulting from stroke and an important determinant of the long-term consequences of this disorder. The cell death that leads to infarct formation is likely to be the result of multiple interacting pathol. processes. A range of factors, including the severity of the ischemic insult and whether this is permanent or reversed, det. which mechanisms predominate. Although evaluating mitochondrial properties in intact brain is difficult, evidence for several potentially deleterious responses to cerebral ischemia or post-ischemic reperfusion have been obtained from investigations using animal models of stroke. Marked changes in ATP and related energy

metabolites develop quickly in response to occlusion of a cerebral artery, as expected from limitations in the delivery of oxygen and glucose. However, these alterations are often only partially reversed on reperfusion despite improved substrate delivery. Ischemia-induced decreases in the mitochondrial capacity for respiratory activity probably contribute to the ongoing impairment of energy metab. during reperfusion and possibly also to the magnitude of changes seen during ischemia. Conditions during reperfusion are likely to be conducive to the induction of the permeability transition in mitochondria. There are as yet no well-characterized techniques to identify this change in the intact brain. However, the protective effects of some agents that block formation of the transition pore are consistent with both the induction of the permeability transition during early recirculation and a role for this in the development of tissue damage. Release of cytochrome c into the cytoplasm of cells has been obsd. with both permanent and reversed ischemia and could trigger the death of some cells by apoptosis, a process which probably contributes to the expansion of the ischemic lesion. Mitochondria are also likely to contribute to the widely-accepted role of nitric oxide in the development of ischemic damage. These organelles are a probable target for the deleterious effects of this substance and can also act as a source of superoxide for reaction with the nitric oxide to produce the damaging species, peroxynitrite. Further characterization of these mitochondrial responses should help to elucidate the mechanisms of cell death due to cerebral ischemia and possibly point to novel sites for **therapeutic** interventions in stroke.

L85 ANSWER 8 OF 93 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

2002315193 EMBASE Biochemical alterations in cerebrospinal fluid during thoracoabdominal aortic cross-clamping in dogs. Nagy G.; Dzsinich Cs.; Selmeci L.; Sepa G.; Dzsinich M.; Kekesi V.; Juhasz-Nagy A.. Dr. G. Nagy, Department of Cardiovascular Surgery, Semmelweis University Budapest, Varosmajor u. 68., Budapest, Hungary. Annals of Vascular Surgery 16/4 (436-441) 2002.
Refs: 23.
ISSN: 0890-5096. CODEN: AVSUEV. Pub. Country: United States. Language: English. Summary Language: English.

AB Spinal cord damage during and after thoracoabdominal aortic cross-clamping continues to be a major problem. Somatosensory and motor evoked potentials have been used to monitor spinal cord function but their value for predicting paraplegia has been controversial. The aim of this study was to measure biochemical markers in the cerebrospinal fluid (CSF) and correlate changes with spinal cord **ischemia**. Since neural **tissue** utilizes only glucose as substrate for its metabolism and energy supply, we measured changes of **metabolites** of anaerobe glycolysis. In a canine model in which general anesthesia was used, the thoracoabdominal aorta was cross-clamped proximally and distally for 60 min. Hemodynamic parameters, blood gases, and glucose level were monitored continuously. Blood and CSF sampling were performed at baseline, at 15, 30, and 55 min during cross-clamping, and at 5 and 15 min after aortic declamping. Levels of lactate (1.7 .+-. 0.1 to 3.2 .+-. 0.3 mmol/l), pCO(2) (43 .+-. 2 to 35 .+-. 1.6 mmHg), and neuron-specific enolase (NSE) (5.17 .+-. 0.5 to 13.0 .+-. 3.5 .mu.g/L) in CSF showed significant changes ($p < 0.05$) during clamping and reperfusion. Changes in CSF lactate and NSE levels correlate with the duration of spinal cord ischemia. These markers of ischemic metabolism appear suitable to monitor the degree of spinal cord ischemia during thoracoabdominal cross-clamping and may be useful to predict the efficacy of **preventive** methods.

L85 ANSWER 9 OF 93 MEDLINE

2002445397 Document Number: 22131223. PubMed ID: 12135593. Limited

Searched by: Mary Hale 308-4258 CM-1 1E01

effects of micronutrient supplementation on strength and physical function after abdominal aortic aneurysmectomy. Watters James M; Vallerand Andrew; Kirkpatrick Susan M; Abbott Heather E; Norris Sonya; Wells George; Barber Graeme G. (Department of Surgery, University of Ottawa, Canada.) CLINICAL NUTRITION, (2002 Aug) 21 (4) 321-7. Journal code: 8309603. ISSN: 0261-5614. Pub. country: Scotland: United Kingdom. Language: English.

AB BACKGROUND: **Tissue** injury following **ischemia** -reperfusion is mediated in part by free oxygen radicals. We hypothesized that perioperative micronutrient supplementation would augment antioxidant defenses, minimize muscle injury, and minimize postoperative decreases in muscle strength and physical function following abdominal aortic aneurysmectomy. SETTING: A university-affiliated hospital and regional referral center. DESIGN: A randomized, double-blind, placebo-controlled trial of supplementation with beta-carotene, vitamins C and E, zinc, and selenium for a period of 2-3 weeks prior to surgery and 1 week thereafter. STUDY POPULATION: Patients undergoing elective abdominal aortic aneurysmectomy (n=18 per group). PRINCIPAL MEASUREMENTS: Handgrip and other measures of strength and physical function. RESULTS: Handgrip and quadriceps strength decreased following surgery, but not to a significantly different extent in the placebo and supplemented groups. Self-rated physical function decreased following surgery in the placebo group and was preserved in the supplemented group. CONCLUSIONS: Perioperative supplementation with micronutrients with antioxidant properties has limited effects on strength and physical function following major elective surgery.

L85 ANSWER 10 OF 93 CAPLUS COPYRIGHT 2003 ACS

2002:229161 Document No. 137:75392 1H-MRS study of the metabolite on the border zone of acute cerebral ischemia. Yi, Li; Lu, Guang; Liu, Mai-li; Zhang, Su-ming (State Key Lab. of Magnetic Resonance and Atomic and Mol. Physics, Wuhan Inst. of Physics and Mathematics, The Chinese Academy of Sciences, Wuhan, 430071, Peop. Rep. China). Bopuxue Zazhi, 19(1), 1-7 (Polish) 2002. CODEN: BOZAE2. ISSN: 1000-4556. Publisher: Kexue Chubanshe.

AB Objective: The use of different models of focal cerebral ischemia to appraise the time-space rules of 1H-MRS on measuring metab. and energy changes in the post-**ischemia** brain **tissue** provides the clin. doctors with valuable information to judge the prognosis and carry out more effective **therapy** from the biochem. point of view. Methods: 9 healthy Sprague-Dawly rats (indiscriminate the sex) was divided into two groups randomly. Group A (4 rats), occluded with self-thrombus for 1 h; Group B (5 rats), occluded with thread-emboli for 1 h. The 1H-MRS was examd. in 30, 40, 50, 60 min after occlusion resp., and the metabolic changes of NAA, Cho and Lac in the regions of interest in partly-fixed quantity were analyzed. Results: Set the resonance integrated area ratio of NAA, Cho, Lac to Pcr + Cr as the criterion, the values of all the **metabolites** declined gradually within 1 h after ischemia. Esp., the ratio of Cho/(Pcr + Cr). NAA/(Pcr + Cr)and Lac/(Pcr + Cr)in 60 min has significant difference from that in 50 min (P < 0. 05). Conclusions: Magnetic Resonance Proton Spectroscopy is a good research tool, which is straight-forward, comprehensive and no damage, for the study of cellular metab. and the status of the biochem. energy in acute ischemia stroke.

L85 ANSWER 11 OF 93 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

2001:267951 Document No.: PREV200100267951. Diabetes-induced changes in renal tissue oxygen tension and cellular metabolism: Influence of polyol pathway. Palm, Fredrik (1); Hansell, Peter (1); Ronquist, Gunnar (1); Waldenstrom, Anders (1); Liss, Per (1); Carlsson, Per-Ola (1). (1) Department of Physiology, Biomedical Center, Uppsala University,

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Husargatan 3, Uppsala, SE 75123 Sweden. FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A447. print. Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001 ISSN: 0892-6638. Language: English. Summary Language: English.

AB This study aimed to characterize the influence of insulin-deficient (streptozotocin-induced) diabetes mellitus on regional renal blood perfusion and tissue oxygen tension. Laser-Doppler flowmetry was used to measure local blood flow, whereas oxygen tension was recorded with Clark-type microelectrodes. A marked blood flow gradient existed between the cortical and medullary region in all animals, but there were no differences between diabetic and non-diabetic rats. The oxygen tension profile with values recorded each mm from cortex to papilla was 47+-6, 25+-7, 43+-4, 33+-4 and 24+-7 mm Hg in non-diabetic animals (n=12). In comparison, animals diabetic for 4 weeks had apprx35 % lower oxygen tension values at all corresponding depths. The decrease in oxygen tension was more pronounced in the medullary region and **preventable** by daily administration of the aldose reductase inhibitor AL-1576 throughout the course of diabetes. Decreased oxygen tension was not related to **tissue ischemia**, as evaluated by measurements of purine **metabolites** in separate microdialysis experiments. However, a marked increase in lactate/pyruvate ratio in both cortex and medulla of diabetic animals existed (26.7+-8.0 compared to 53.5+-7.7 in the cortex and 17.4+-7.7 compared to 35.6+-30.3 in medulla in non-diabetic and diabetic animals, respectively). Only the increase in lactate/pyruvate ratio in the medulla could be **prevented** by AL-1576 **treatment**. In conclusion, diabetic animals displayed decreased tissue oxygen tension and increased lactate/pyruvate ratio throughout the kidney compared to non-diabetic animals, despite similar regional renal blood flow. In the medullary region these disturbances seem to be mediated through increased polyol pathway activity and to be **preventable** by inhibiting the enzymatic activity of aldose reductase.

L85 ANSWER 12 OF 93 MEDLINE DUPLICATE 2

2001406165 Document Number: 21349905. PubMed ID: 11457651. Topically applied liposome encapsulated superoxide dismutase reduces postburn wound size and edema formation. Vorauer-Uhl K; Furnschlief E; Wagner A; Ferko B; Katinger H. (Institute of Applied Microbiology, University of Agricultural Sciences, Muthgasse 18, A-1190, Vienna, Austria.. k.vorauer@iam.boku.ac.at) . EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, (2001 Aug) 14 (1) 63-7. Journal code: 9317982. ISSN: 0928-0987. Pub. country: Netherlands. Language: English.

AB The overproduction of biochemical mediators, and activation of leukocytes and endothelial cells, generated in thermally injured tissue, gives rise to both local and distant effects. The formation of short-lived, highly reactive **metabolites**, such as oxygen free radicals, increases with increasing **tissue ischemia**, and causes further cell damage. Human recombinant Cu/Zn-superoxide dismutase (rh-Cu/Zn-SOD), an enzyme which captures these radicals, may have a beneficial effect on the postburn inflammation processes. In this study, the influence of rh-Cu/Zn-SOD application to thermally injured tissue of rabbit backskin was examined. Three different delivery strategies were compared, pure or liposomally encapsulated enzyme, or intralesionally injected rh-Cu/Zn-SOD. For control, one animal group was **treated** with plain gel and another group was kept untreated. At 24 h following trauma a statistically significant difference in lesion sizes between the enzyme **treated** and control groups was observed. After 72 h tissue swelling had diminished significantly more in the rh-Cu/Zn-SOD **treated** groups as compared to the control animals. The best results were achieved by spreading liposomes encapsulating the enzyme onto

the wounds. Our results suggest that local **treatment** of burn wounds with enzymatic radical scavengers such as rh-Cu/Zn-SOD has a beneficial effect on the extent of the postburn damage.

L85 ANSWER 13 OF 93 CAPLUS COPYRIGHT 2003 ACS
2000:573661 Document No. 133:172201 Felbamate derived compounds. MacDonald, Timothy L.; Miller, Thomas A.; Thompson, Charles D. (University of Virginia Patent Foundation, USA). PCT Int. Appl. WO 2000047202 A1 20000817, 44 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US3147 20000208. PRIORITY: US 1999-PV119254 19990209; US 1999-PV136881 19990601; US 1999-PV137204 19990602.
AB The present invention relates to novel felbamate derivs. and their use to **treat** neurol. diseases such as epilepsy and to **treat** tissue damage resulting from ischemic events. The felbamate derivs. are modified to **prevent** the formation of **metabolites** that are believed responsible for the toxicity assocd. with felbamate **therapy**.

L85 ANSWER 14 OF 93 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-452360 [39] WPIDS
AB WO 200039070 A UPAB: 20000818
NOVELTY - Ortho-diphenol derivatives (I), are new.
DETAILED DESCRIPTION - Ortho-diphenol derivatives of formula (I), their salts, hydrates, esters, solvates, prodrugs, **metabolites** and/or stereoisomers, are new.
A = O or S;
R = 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, aryl, heteroaryl, carbocyclyl or heterocyclyl, each optionally substituted by at least one Q;
D' = bond, or 1-3C alkyl, 2-3C alkenyl or 2-3C alkynyl each having any C optionally replaced with O, N or S and optionally substituted by at least one Q;
X = aryl, heteroaryl, carbocyclyl or heterocyclyl, each optionally substituted by at least one Q;
Q = OH, halogen, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, amino, imino, alkylamino, arylamino, arylazo, arylthio, aminoalkyl, sulfhydryl, thioalkyl, alkylthio, sulfonyl, 1-6C alkyl, 2-6C alkenyl or alkynyl, aryl, aralkyl, heteroaryl, carbocyclyl or heterocyclyl;
provided that:
(1) when R = methyl and D' = bond, then X does not equal phenyl, 4-nitrophenyl, 4-phenylazo-phenyl or 3,5-dinitrophenyl;
(2) when R = substituted **benzopyran** and D' = bond, ethenyl or NH, then X does not equal phenyl or 3,4,5-trihydroxyphenyl;
(3) when R and D' = ethenyl, then X does not equal 4-hydroxy-3-methoxyphenyl;
(4) when R = methyl and D' = ethenyl, then X does not equal 2-hydroxyphenyl;
(5) when R = 1-hydroxy-2-alkylaminoethyl and D = bond, then X does not equal phenyl, methylphenyl or 4-methoxyphenyl; and
(6) when R = propenyl and D' = bond, then X does not equal phenyl.
ACTIVITY - Neuroprotective; vasotropic; nootropic; antiparkinsonian; anticonvulsant; cerebroprotective; cardiovascular; cardiant; antianginal;

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ophthalmological; anti-HIV; immunomodulator; antiarthritic; antiarteriosclerotic; muscular; cytostatic; antidiabetic; tranquilizer; vulnerary; antiinflammatory; gastrointestinal; osteopathic; analgesic; nephrotropic; antibacterial; immunosuppressive; dermatological.

MECHANISM OF ACTION - Poly ADP (adenosine diphosphate) ribose polymerase inhibitor.

(I) have IC50 values of at most 100 (preferably at most 25, especially at most 1) micro M for inhibiting poly ADP ribose polymerase in vitro.

USE - (I) are useful for the **treatment** of tissue damage resulting from cell damage or death due to necrosis or apoptosis, neuronal mediated tissue damage or diseases, neural **tissue** damage resulting from **ischemia** and reperfusion injury, neurological and neurodegenerative diseases (particularly Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotropic lateral sclerosis), vascular stroke, cardiovascular disorders (particularly tissue damage, coronary artery disease, myocardial infarction, angina pectoris and cardiogenic shock), age-related macular degeneration, AIDS and other immune diseases, arthritis, atherosclerosis, cachexia, cancer, degenerative diseases of skeletal muscle involving replicative senescence, diabetes, head trauma, immune senescence, inflammatory bowel disorders (particularly colitis or Crohn's disease), muscular dystrophy, osteoarthritis, osteoporosis, chronic, acute or neuropathic pain, nervous insult, peripheral nerve injury, renal failure, retinal ischemia, septic shock and skin aging, diseases or disorders relating to life span or proliferative capacity of cells, diseases or conditions induced or exacerbated by cellular senescence, and demyelinating diseases such as multiple sclerosis (claimed). (I) can be used for inhibiting poly ADP ribose polymerase activity, altering gene expression or radiosensitizing (claimed). Cancers which can be **treated** with (I) include adrenocorticotrophic hormone (ACTH) producing tumors, acute lymphocytic or non-lymphocytic leukemia, cancer of the adrenal cortex, bladder, brain, gall bladder, head and neck, kidney, liver, lung (small and non-small cell), ovary, prostate, pancreas, penis, skin, stomach, thyroid, uterus, vagina, vulva, breast or cervix, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, cutaneous T-cell lymphoma, endometrial cancer, esophageal cancer, Ewing's sarcoma, hairy cell leukemia, Hodgkin's lymphoma, Kaposi's sarcoma, malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, non-Hodgkin's lymphoma, osteosarcoma, retinoblastoma, soft-tissue sarcoma, squamous cell carcinomas, testicular cancer and Wilm's tumor (claimed). Dwg.0/2

L85 ANSWER 15 OF 93 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-450972 [39] WPIDS
CR 1994-332829 [41]; 2001-101733 [11]; 2002-088855 [12]
AB US 6077837 A UPAB: 20020730

NOVELTY - Conjugation of active agents to intracellular transport agents by covalent bonding susceptible to enzymatic cleavage within the cell to release the agent is new.

DETAILED DESCRIPTION - Method for **treating** a disease or disorder in mammals related to elevated levels of intracellular enzyme activity comprises administration of a prodrug (I) consisting of an active protein kinase inhibitor covalently bonded to an intracellular transporting adjuvant such that the prodrug is cell-membrane permeable and the covalent bond is cleavable in the presence of elevated levels of enzyme activity to provide accumulated amounts of the active agent within the cell.

USE - (I) are useful in the **treatment** of localized **tissue ischemia**, stoke, epilepsy, asthma and allergy.

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Because hyperactivity of enzymes is associated with uncontrolled growth, (I) are potentially useful in the **treatment** cancers.

ADVANTAGE - (I) are able to target malfunctioning cells and are activated to release the active agent by the elevated levels of enzymes in them. The active agent is generally not permeable to the cell wall so becoming trapped and concentrated within the target cell for greater effectiveness.

Dwg.0/0

L85 ANSWER 16 OF 93 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-374331 [32] WPIDS
CR 2001-272595 [28]
AB US 6045826 A UPAB: 20030429

NOVELTY - Water soluble composition (A) comprises a bioactive lipophilic compound and a solubilizing agent (I).

DETAILED DESCRIPTION - Water soluble composition (A) comprises a bioactive lipophilic compound and a solubilizing agent of formula (X-OOC-((CH2)n-COO)m)p-Y. (I).

X = a residue of a hydrophobic sterol, tocopherol or their derivatives;

Y = a residue of a hydrophilic polyether, polyalcohol or their derivatives;

p = 1 or 2;

m = 0 or 1 and

n = 0-18,

provided that when p and m are 1 and the hydrophobic group is cholesterol, n is between 4 and 8 and when p and m are 1 and the hydrophobic group is (+)- alpha -tocopherol, n is not 2.

INDEPENDENT CLAIMS are included for the following:

(1) preparation of (A) which comprises heating a mixture of the lipophilic compound and (I) in a predetermined molar ratio to give a clear melt and recovering (A);

(2) preparation of (A) which comprises dissolving the lipophilic compound and (I) in a predetermined molar ratio in a water soluble organic solvent, diluting the solution with water and removing the organic solvent and optionally water solution of the lipophilic compound and solubilizing agent with water and removing the solvent;

(3) purifying a water soluble composition which comprises dissolving the composition in not more than 2 volumes of water, heating the solution to separate the water-soluble composition as a liquid phase and separating the liquid phase from the hot solution while maintaining the temperature unchanged;

(4) a pharmaceutical or cosmetic composition comprising a bioactive lipophilic compound in the form of (A) and an additive or vehicle comprising solvents, adjuvants, sweeteners, fillers, flavorants, lubricants, binders, moisturizing agents and/or preservatives;

(5) **treatment** of a medical disorder associated with oxidative tissue damage or mitochondrial dysfunction which comprises administration of (A) containing coenzyme Q10 as the lipophilic compound;

(6) **treating** a fungal infection which comprises administration of (A) comprising a macrolide polyene antibiotic as the lipophilic compound and

(7) preparation of a water soluble composition of coenzyme Q10 which comprises dissolving coenzyme Q10 in (I).

USE - Useful for **treating** disorders related to tissue damage caused by free radicals and oxidants and/or mitochondrial dysfunction including cardiovascular diseases, muscular disorders, mitochondrial encephalomyolopathies and neurodegenerative disorders, restoration of immune deficiencies caused by drugs or infections and minimizing **tissue** damage resulting from **ischemia** and

reperfusion. The coenzyme Q10 is also used as an adjuvant for **treating** infectious diseases, in combination with cholesterol lowering agents for **treating** hypercholesteremia, in combination with chemotherapeutic agent for **treating** cancers and in cosmetics for slowing skin ageing.
Dwg.0/5

L85 ANSWER 17 OF 93 MEDLINE DUPLICATE 3
2001176032 Document Number: 21032713. PubMed ID: 11186327.
Therapeutic angiogenesis: a case for targeted, regulated gene delivery. Webster K A. (Department of Molecular and Cellular Pharmacology, University of Miami Medical Center, FL 33136, USA.) CRITICAL REVIEWS IN EUKARYOTIC GENE EXPRESSION, (2000) 10 (2) 113-25. Ref: 71. Journal code: 9007261. ISSN: 1045-4403. Pub. country: United States. Language: English.
AB Blood and vascular disorders underlie a plethora of pathological conditions and are the single most frequent cause of human disease. Eliminated or restricted blood flow to tissues as a result of vessel dysfunction results in the disruption of oxygen and nutrient delivery and the accumulation of waste **metabolites**. Cells cannot survive extended severe ischemia but may be able to adapt to a moderate condition where diffusion to and from bordering nonischemic regions sustain vital functions. Under this condition, secondary functions of affected cells are likely to be impaired and a new metabolic equilibrium is established, determined by the level of cross-diffusion. In tissues with a normally high metabolic turnover such as skeletal and cardiac muscle, ischemia causes hypoxia, acidosis, and depressed function (contractility). The **treatment** possibilities for **tissue ischemia** resulting from vascular disease are limited. Lipid-lowering agents may help slow the progression of vessel disease in some instances, but surgical reconstruction may be the only option in advanced stages, and even this is not always an option. An alternative and rather obvious strategy to **treat** ischemia is to activate endogenous angiogenic or vasculogenic pathways and stimulate revascularization of the tissue. The feasibility of such a strategy has now been established through the results of studies over the past decade and a new discipline called **therapeutic** angiogenesis has emerged. This review focuses on the application of **therapeutic** angiogenesis for **treating** peripheral limb ischemia and coronary artery diseases; the author traces the evidence supporting the feasibility of this **treatment** strategy, its current limitations, and possible directions.

L85 ANSWER 18 OF 93 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
2000353364 EMBASE Intraarterial thrombolysis for acute ischemic stroke.
Budzik R.F. Jr.; Pergolizzi R.S.; Putman C.M.. Dr. R.F. Budzik Jr., Interventional Neuroradiology, Department of Radiology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114-2696, United States.
Seminars in Neurosurgery 11/1 (107-132) 2000.
Refs: 102.
ISSN: 1526-8012. CODEN: SNEEAH. Pub. Country: United States. Language: English. Summary Language: English.
AB Stroke affects more than 700,000 people each year in the United States and is the third leading cause of death behind heart disease and cancer. It is the leading cause of health care dollar expenditure and the most common cause of disability resulting in rehabilitation and nursing home admissions1. Despite a decline in stroke mortality in some countries,1 there is little evidence for a decline in incidence.2 Due to anticipated demographic changes from an aging population, the incidence of stroke is expected to increase, causing an even greater need to find effective **treatments**.3 Stroke is a clinical event defined as an acute onset of neurologic deficit in which maximal dysfunction is reached rapidly and

in which delayed neurologic deterioration does not occur unless additional complications arise. Cerebrovascular occlusion due to embolus or thrombosis accounts for 75% of strokes.4 The vascular occlusion causes **tissue** oligemia with **ischemia** resulting in neuronal dysfunction and clinical stroke. Twenty percent of patients with thromboembolic stroke die in the first month after the event.5 Outcome for survivors can be devastating. About two-thirds have decreased vocational and social function, half have peripheral motor weakness, one-third have marked inability to perform activities of daily living, and one-sixth require institutional care.6 Patients with proven occlusions of the main trunk of the middle cerebral artery have initial mortality rates as high as 25 to 40%.7-9 Patients with less severe middle cerebral artery (MCA) branch occlusions have been shown to have 3-month mortality as high as 14.3%.10 Even more devastating, basilar occlusions are generally thought to have an 80-90% mortality rate without **treatment**. Prior to the United States (U.S.) Food and Drug Administation's (FDA) approval of intravenous tissue plasminogen activator (tPA) for acute stroke in 1995, no approved direct **therapeutic** intervention was available for acute stroke in the U.S. Care was predominately supportive, with a prevailing attitude among health care providers that the damage was completed. Indirect strategies to **treat** thromboembolic stroke targeted the management of potential complications and attempted to reverse or stabilize neurologic impairment. Management of concurrent medical conditions was undertaken in an attempt to minimize brain injury. Anticoagulation agents were used to reverse or **prevent** progression of thrombus formation. Neuroprotective agents have been postulated to protect viable neurons from ongoing damage by toxic **metabolites** formed by ischemia. Although these approaches have begun to unravel the complexities of **treating** acute stroke by managing various aspects of stroke evolution, none has proven particularly effective and none have directly approached the inciting vascular occlusion. The development of and experience with thrombolytic agents has recently created great interest in directing stroke **therapy** at the site of thromboembolic vascular occlusion. Success of peripherally administered intravenous thrombolytic trials have culminated in the FDA approval of recombinant-tPA as the first effective **treatment** of stroke.11 Concurrently, advances in catheter technology for endovascular navigation have enabled direct access to the site of cerebrovascular occlusion and have the potential to provide the next step for effective **treatment** of thromboembolic stroke. Intra-arterial delivery of thrombolytic agents has been used for several years for acute ischemic stroke with some initial success, and has become the standard for selected patients at many institutions. Our purpose is to examine newer clinical and technical aspects of this promising neurointerventional **treatment**, to review past experience with intra-arterial thrombolysis, and to discuss current **treatment** protocols and future developments.

L85 ANSWER 19 OF 93 CAPLUS COPYRIGHT 2003 ACS

1999:354404 Document No. 131:23519 Mitochondrially targeted compounds. Murphy, Michael Patrick; Smith, Robin A. J. (University of Otago, N. Z.). PCT Int. Appl. WO 9926582 A2 19990603, 35 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-NZ172 19981125. PRIORITY: NZ 1997-329255 19971125.

Searched by: Mary Hale 308-4258 CM-1 1E01

AB The title compds. comprise a lipophilic cation covalently coupled to a **therapeutically** or prophylactically useful compd. such as an antioxidant. The lipophilic cation is preferably triphenylphosphonium, and the compd. is of the form Ph3P+XR Z- (X = linking group; Z = anion; R = antioxidant moiety). Pharmaceutical compns. contg. mitochondrially targeted antioxidants are useful for patients who would benefit from reduced oxidative stress, e.g patients with degenerative diseases such as parkinsonism, Alzheimer's disease , Huntington's chorea, and **ischemia**-reperfusion **tissue** injury. Thus, a mitochondrially targeted **vitamin E** deriv. (I) was prepd. by reaction of 2-(2-bromoethyl)-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-**benzopyran** with PPh3. I-3H was rapidly and selectively accumulated by rat liver mitochondria in vitro under conditions which generated a mitochondrial membrane potential of .apprx.180 mV with an accumulation ratio of .apprx.6000. The I IC50 for inhibition of lipid peroxidn. in rat brain homogenates was 210 nM.

L85 ANSWER 20 OF 93 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
1999:184142 Document No.: PREV199900184142. Use of 3,4-diphenyl **chromans** for the manufacture of a pharmaceutical composition for vasodilatory **treatment** or **prophylaxis**. Korsgaard, N.; Shalmi, M.; Weis, J. U.; Guldhammer, B. H.. Vaerlose Denmark. ASSIGNEE: NOVO NORDISK A-S. Patent Info.: US 5886021 March 23, 1999. Official Gazette of the United States Patent and Trademark Office Patents, (March 23, 1999) Vol. 1220, No. 4, pp. 3573. ISSN: 0098-1133. Language: English.

L85 ANSWER 21 OF 93 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-116306 [10] WPIDS
AB WO 9959973 A UPAB: 20011206
NOVELTY - Carboxamide compounds (I) and their salts, hydrates, esters, solvates, prodrugs, **metabolites** and/or stereoisomers are new.

DETAILED DESCRIPTION - Carboxamide compounds of formula (I) and their salts, hydrates, esters, solvates, prodrugs, **metabolites** and/or stereoisomers are new.

Y = fused 5-6 (non)aromatic, carboxylic or O, S, N-containing heterocyclic, where Y and any heteroatom(s) are optionally substituted by non-interfering (cyclo)alkyl, (cyclo)alkenyl, aralkyl, aryl, carboxy and/or halo;

X is at the 1-position of ring Y and is COOR5 or an optionally substituted P(O)(OH)NH2, P(O)(OH)OEt, SO3H, SO2NH(R7) or a group of formula (a)-(c);

R7, R1 = H, (cyclo)alkyl, (cyclo)alkenyl optionally substituted (cyclo)alkyl or (cyclo)alkenyl; and

R2-R5 = H, (cyclo)alkyl, (cyclo)alkenyl, aralkyl, aryl, amino, hydroxyl, 1-piperazine, 1-piperidine or 1-imidazoline, optionally substituted (alkoxy, phenoxy, benzyloxy, (cyclo)alkyl, (cyclo)alkenyl, hydroxy, carboxy, carbonyl, amino, amido, (iso)cyano, nitro, nitroso, (iso)nitrile, imino, azo, diazo, sulfonyl, sulfoxy, thio, thiocarbonyl, sulfhydryl, (halo)alkyl, trifluoromethyl, aralkyl or aryl);

provided that if Y is a fused, 6-membered aromatic carbocyclic ring, R1-R4 are H and X is not COOH.

An INDEPENDENT CLAIM is also included for the preparation of (I).

ACTIVITY - Anti-HIV; cytostatic; antiinflammatory; cardiant; antidiabetic; antibacterial; immunosuppressive; osteopathic; antiarteriosclerotic.

Male Wistar rats (250-300 g) were anesthetized with 4% halothane and maintained with 1.0-1.5% halothane until the end of surgery. The animals were maintained in a warm environment during recovery from anesthesia. 2 Hours later they were re-anesthetized. The animals are allowed to survive for 24 hours with free access to food and water, and were sacrificed. The

brains were immediately removed, frozen on dry ice and stored at -80 deg. C. Selective sections of the brain were cut, stained with cresyl violet according to Nissl procedure, and examined. (I) was administered in a single dose or series of multiple doses, as i.p or i.v, at different times, both before and after the onset of ischemia. One was found to provide 20-80% protection from focal cerebral ischemia. Female Sprague-Dawley rats (each 300-350 g) were anesthetized with intraperitoneal ketamine at a dose of 150 mg/kg. The rats were endotracheally incubated and ventilated with oxygen-enriched room air. The rat chests were opened by median sternotomy, to determine the ischemic risk region. The hearts were then arrested with potassium chloride and cut into five transverse slices. Each slice was weighed and incubated in 1% solution of trimethyltetrazolium to visualize the infarcted myocardium located within the risk region. (I) was administered as a single or a series of multiple doses, as i.p or i.v at different times, both before and after the onset of ischemia. (I) was found to have 10-40% ischemia/reperfusion injury protection.

MECHANISM OF ACTION - Inhibitors of poly(adenosine 5'-diphospho-ribose) polymerase (PARP) activity.

8-Carbamoyl-naphthalene-carboxylic acid (Ia) exhibited an IC50 value of 0.25 micro M for the inhibition of recombinant human PARP.

USE - For effecting a neuronal activity not mediated by NMDA toxicity, **treating** arthritis, diabetes, inflammatory bowel disorder, cardiovascular disorder, septic shock, cancer, radiosensitizing tumor cells (where the tumor cells are ACTH-producing tumors, acute (non)lymphocytic leukemia, cancer of the adrenal cortex, bladder, brain, breast and cervix cancer, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, Ewing's sarcoma, gallbladder cancer, hairy cell leukemia, head and neck cancer, Hodgkin's lymphoma, Kaposi's sarcoma, kidney, liver and lung (small and/or non-small cell) cancers, malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, skin cancer, soft tissue sarcoma, squamous cell carcinomas, stomach cancer, testicular cancer, thyroid cancer, trophoblastic neoplasms, cancer of the uterus, vaginal cancer, cancer of the vulva and Wilm's tumor), ischemia, to extend the life span and proliferative capacity of cells, altering gene expression of senescent cells, skin aging, neurological disorders, muscular dystrophy, age related macular degeneration, immune senescence or AIDS (claimed). For **treating** or **preventing** tissue damage resulting from cell damage or death due to necrosis or apoptosis, neuronal mediated tissue damage, neural **tissue** damage resulting from **ischemia** and reperfusion injury, neurodegenerative diseases and vascular stroke (claimed).

Cardiac reperfusion injury in a patient with a new donated heart was **prevented** by intracardiac administration of (I). 1-Carboxynaphthalene-1-carboxamide (Ib) when intraperitoneally administered provided 40% protection against mortality from septic shock. Radiosensitization (before radiation **therapy** during cancer **treatment**) by administering (I) was found to make the tumor more susceptible to radiation **therapy**. Increase in elastin expression of mRNA senescent cell with the administration of (I) was increased in comparison to the control.

ADVANTAGE - 8-carbamoyl-naphthalene carboxylic acid (Ia) had IC50 of 100 M (preferably 25 M) or lower for inhibiting poly(ADP-ribose) polymerase in vitro (claimed).

Dwg.0/2

L85 ANSWER 22 OF 93 WPIDS (C) 2003 THOMSON DERWENT
AN 1999-419237 [35] WPIDS
CR 2002-537173 [57]

Searched by: Mary Hale 308-4258 CM-1 1E01

AB WO 9934792 A UPAB: 20020910
NOVELTY - A **treatment** of **ischemia** and **preventing** subsequent **tissue** damage using MEK1 inhibitors is new.

DETAILED DESCRIPTION - A **treatment** of ischemia comprises administering an MEK1 inhibitor in sufficient quantity to alleviate the symptoms associated with excess of MEK1 activity.

INDEPENDENT CLAIMS are included for:

(1) a pharmaceutical composition comprising an MEK1 inhibitor and a non -MEK1 inhibitor anti-stroke agent;

(2) a kit comprising an MEK1 inhibitor with instructions for use in the **treatment** of an ischemic condition; and

(3) a medical product comprising a perfusion fluid containing an MEK1 inhibitor optionally containing an isolated organ.

ACTIVITY - **Ischemia**-induced **tissue** damage protectant; neuroprotectant.

Mice were pretreated with intracerebroventricular injections of PD98959(200 micro l) (an MEK1 inhibitor) or dimethylsulfoxide (0.4%)(control) 30 minutes before an induced focal cerebral ischemia. The neural damage after 22 hours was measured by tetrazolium chloride staining. The neuroprotective ability of the drug was dose dependent with a 23% decrease in damage after a 50 micro M dose and a 42% decrease after the 100 micro M dose. A dose of 200 micro M resulted in a 43% decrease in damage seen after 3 days.

MECHANISM OF ACTION - Specific MEK1 kinase inhibitors bind to MEK1 proteins or inhibit their expression.

USE - For the **prevention** of **tissue** damage following **ischemia** and subsequent reperfusion in conditions such as stroke and organ transplantation (e.g. heart, kidney, pancreas, lung and intestines) and neural surgery. The method may also be used prophylactically for patients at risk of stroke and to **treat** the symptoms of a proliferative disease.

ADVANTAGE - None given.

Dwg.0/0

L85 ANSWER 23 OF 93 WPIDS (C) 2003 THOMSON DERWENT
AN 1999-214692 [18] WPIDS
CR 1999-205125 [17]; 1999-214688 [17]; 1999-214693 [17]; 1999-228970 [17]; 1999-243599 [20]; 1999-276930 [18]; 2000-116307 [06]
AB WO 9911644 A UPAB: 20011206
NOVELTY - Triheterocyclic compounds (I) are new. DETAILED DESCRIPTION - Tri-N-heterocyclic compounds of formula (I) and their salts, esters, prodrugs and **metabolites** are new. Y = a group forming a fused 5 or 6 membered aromatic or non-aromatic heterocyclic ring containing at least one N heteroatom in a 1,3-relationship with the N atom in (I) and Y is optionally substituted by alkyl, alkenyl, cycloalkyl, cycloalkenyl, aralkyl, aryl, O , CO2R5, SO3H, P(=O)(NH2)OH, P(=O)(OR7)OH, SO2NHR7 or a group of formula (a)-(c) and R5, R7 = H, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aralkyl or aryl, provided that when Y forms a 5 membered unsaturated ring it is substituted by at least one substituent other than H or phenyl.

USE - (I) are used to **treat** or **prevent** tissue damage resulting from cell damage or death due to necrosis or apoptosis, neuronal mediated tissue damage or diseases, neural **tissue** damage resulting from **ischemia** and reperfusion injury, neurological disorders and neurodegenerative diseases, vascular stroke, cardiovascular disorders, age-related macular degeneration, AIDS and other immune senescence diseases, arthritis, atherosclerosis, cachexia, cancer, degenerative diseases of skeletal muscle involving replicative senesence, diabetes, head trauma, immune senescence, inflammatory bowel disorders

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(e.g. colitis or Crohn's disease) , muscular dystrophy, osteoarthritis, osteoporosis, chronic pain, acute pain, neuropathic pain, nervous insult, peripheral nerve injury, renal failure, retinal ischemia, septic shock (e.g. endotoxic shock) and skin ageing, diseases or disorders relating to lifespan or proliferative capacity of cells and diseases induced or exacerbated by cellular senescence or to radiosensitize hypoxic tumor cells. (I) are used to **treat** or **prevent** cardiovascular tissue damage resulting from cardiac ischemia or reperfusion injury e.g. reperfusion injury occurring at the termination of cardiac bypass procedures or during cardiac arrest. (I) are also used to **treat** cardiovascular disorders such as coronary artery disease, myocardial infarction, angina pectoris, atherosclerosis and cardiogenic shock. (I) are also used to **treat** neurological disorders including trigeminal neuralgia, glossopharyngeal neuralgia, Bell's palsy, myasthenia gravis, muscular dystrophy, amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies such as those caused by lead, dapsone, ticks, porphyria or Guillain-Barre syndrome, Alzheimer's disease, Huntington's disease, Parkinson's disease and amyotrophic lateral sclerosis. (I) are particularly useful for **treating** peripheral neuropathy caused by physical injury or disease state, head trauma such as traumatic brain injury, physical damage to the spinal cord, stroke associated with brain damage such as vascular stroke associated with hypoxia and brain damage, focal cerebral ischemia, global cerebral ischemia and cerebral reperfusion injury, demyelinating diseases such as multiple sclerosis and disorders of neurodegeneration. (I) are used to **treat** cancer and to radiosensitize tumor cells in cancers such as ACTH-producing tumors, acute lymphocytic leukaemia, acute nonlymphocytic leukemia, cancer of the adrenal cortex, bladder cancer, brain cancer, breast cancer, cervical cancer, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, esophageal cancer, Ewing's sarcoma, gallbladder cancer, hairy cell leukemia, head and neck cancer, Hodgkin's lymphoma, Kaposi's sarcoma, kidney cancer, liver cancer, lung cancer (small and/or non-small cell), malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, non-Hodgkin's lymphoma, osteosarcoma, ovarian cancer, ovary (germ cell) cancer, prostate cancer, pancreatic cancer, penile cancer, retinoblastoma, skin cancer, soft-tissue sarcoma, squamous cell carcinomas, stomach cancer, testicular cancer, thyroid cancer, trophoblastic neoplasms, uterine cancer, vaginal cancer, cancer of the vulva and Wilm's tumor. ACTIVITY - None given. MECHANISM OF ACTION - Poly(ADP-ribose) inhibitors. (I) have an IC50 of at most 100 mu M for inhibiting PARP.
Dwg.0/2

L85 ANSWER 24 OF 93 WPIDS (C) 2003 THOMSON DERWENT
AN 1999-276930 [23] WPIDS
CR 1999-205125 [17]; 1999-214688 [18]; 1999-214692 [18]; 1999-214693 [18]; 1999-228970 [19]; 1999-243599 [20]; 2000-116307 [10]
AB WO 9911624 A UPAB: 20030619
NOVELTY - Aza-bicyclic compounds (I) are new.
DETAILED DESCRIPTION - Oxo-substituted aza-bicyclic compounds of formula (I) and their base or acid addition salts, hydrates, esters, solvates, prodrugs, **metabolites**, stereoisomers and mixtures are new:
X = O or OH;
R7 = H or lower alkyl, or forms an additional bond to the C carrying X;
Q, Q' = H or together form an additional bond;

Searched by: Mary Hale 308-4258 CM-1 1E01

Y = group completing a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, in which each ring has 5 or 6 members;

Z' = CHR2CHR3; R6C=CR'3; R2C=N; CR2(OH)-NR7; CONR7; or NR9COCHR10;

R2,R3 = H, OH, NH2, NMe2, NO2, piperidine, piperazine, imidazolidine, alkyl, aryl or aralkyl, R2 being in the meta-postion and R3 in the ortho position relative to the ring N;

R'3,R6 = H, lower alkyl, aryl, aralkyl, halo, OH, NH2, dimethylamino, piperidine, piperazine, imidazolidine, NO2, COOR'7 or NR'7R8, R6 being ortho to the ring N;

or R6+R'3 = fused aromatic ring in which each ring has 5 or 6 members;

R'7 = H or lower alkyl;

R9 = H or 1-9C alkyl;

R9,R10 = H, lower alkyl, aryl, aralkyl, halo, OH, piperidine, piperazine, imidazolidine, NO2, COOR'7 or NR'7R8, R10 being ortho to the ring N;

or R9+R10 = fused ring in which each ring has 5-7 members;

alkyl, aryl and aralkyl are optionally substituted by one or more of OH, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, CN, NH2, imino, SH, thioalkyl, COOH, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, NO2, NO and NMe2;

provided that

(a) if X = =O and Z = CHR2CHR3, then R3 is not H or Me;

(b) if X = =O and R6C=CR'3, then R3 is not Me, Ph or (CH2)4-C equivalent to CH;

(c) if R'3 + R6 = fused aromatic ring, then Y is not 1,2-cyclopentylene, 1,2-cyclopent-1-enylene, 3-thia-1,2-cyclopent-1-enylene, 1,2-cyclohexylene, 1,2-cyclohex-1-enylene or 4,5-thia-1,2-cyclohex-1-enylene;

(d) if X,Y and Z' together complete phenanthridone, phenanthridinone, phenanthrene or phenanthridine with an amino or amino alkoxylene group in the 3-position, then the 8-position cannot also be substituted by an amino group or aminoalkoxylene group;

(e) if X = =O, Z' forms a 6-membered unsaturated ring and Y forms a phenyl ring, then the 2-position of the Z'-ring cannot be substituted by H or NO2;

(f) if X = OH or =O and Z' = CH=CH, then Y is not phenyl or 5-hydroxy-phenyl;

(g) if X = =O and Z' = CH=N, then Y is not phenyl; and

(h) if X = =O and Z' = CONH, then Y is not aminophenyl.

INDEPENDENT CLAIMS relate to (i) poly(adenosine diphospho-ribose) polymerase inhibiting pharmaceutical compositions containing or methods using) compounds (I) (including salts etc.) without the provisos (a)-(h) and (ii) the preparation of (I).

ACTIVITY - Neuroprotective; anticancer; cardiovascular; analgesic; antiinflammatory. 3,4-Dihydro-5-(4-(1-piperidinyl)-butoxy)-1(2H)-isoquinolone at 5 mg/kg i.p. gave a significant neuroprotective effect in focal cerebral ischemia tests in rats.

MECHANISM OF ACTION - Poly(adenosine diphospho-ribose) polymerase (poly-(ADP-ribose); PARP) inhibitor. The IC50 value of 5H-1-amino-phenanthridin-6-one in a PARP assay using purified recombinant human PARP from Trevigen was 0.1 mu M.

USE - (I) (including the compounds excluded by the provisos) are used for the **treatment** or **prevention** of:

diseases or conditions such as tissue damage resulting from cell damage or death due to necrosis or apoptosis; neuronal mediated tissue damage or diseases; neural **tissue** damage resulting from **ischemia** and reperfusion injury; neurological disorders and neurodegenerative disease (specifically Alzheimer's, Parkinson's or

Huntington's disease or amyotrophic lateral sclerosis); vascular stroke; cardiovascular disorders (specifically coronary artery disease, angina pectoris, myocardial infarction, cardiogenic shock or cardiovascular tissue damage); age-related macular degeneration; AIDS and other immune senescence diseases; arthritis; atherosclerosis; cachexia; cancer; degenerative diseases of skeletal muscle involving replicative senescence; diabetes; head trauma; inflammatory bowel disorders (specifically colitis or Crohn's disease); muscular dystrophy; osteoarthritis; osteoporosis; chronic, acute or neuropathic pain; nervous insult; peripheral nerve injury; renal failure; retinal ischemia; septic shock; skin aging; diseases or disorders relating to lifespan or proliferative capacity of cells; and diseases or disease conditions induced or exacerbated by cellular senescence (all claimed). They are also used for radiosensitizing tumor cells.

ADVANTAGE - (I) are potent PARP inhibitors, specifically having IC50 below 100 mu M (especially bellow 25 mu M) (claimed); and have reduced side-effects compared with known PARP inhibitors.

Dwg.0/2

L85 ANSWER 25 OF 93 WPIDS (C) 2003 THOMSON DERWENT

AN 1999-214688 [18] WPIDS

CR 1999-205125 [17]; 1999-214692 [17]; 1999-214693 [17]; 1999-228970 [17]; 1999-243599 [20]; 1999-276930 [18]; 2000-116307 [06]

AB WO 9911623 A UPAB: 20020403

NOVELTY - Thioalkyl compounds (I) are new. DETAILED DESCRIPTION - Thioalkyl derivatives of formula (I) and their salts, hydrates, esters, solvates, prodrugs, **metabolites** and/or stereoisomers are new: R1 = lower alkyl, alkenyl or alkynyl; R9, when present = H or lower alkyl; Y = atoms necessary to form a fused, 5-6-membered aromatic or non-aromatic, carbocyclic or heterocyclic ring system; Z = CHR2CHR3, R6C=CR3, R2C=N, CR2(OH)NR7 or C(O)NR7; R2, R3 = H, alkyl, aryl or aralkyl; R6, R3 = H, lower alkyl, aryl, aralkyl, chloro, bromo or NR7R8, or, taken together, form a fused, 5-6-membered aromatic or non-aromatic, carbocyclic or heterocyclic ring system; R7, R8 = H or lower alkyl, provided that when R1 = methyl, R9 is absent, and R6 and R3 form a 6-membered , carbocyclic unsaturated ring; and Y = aromatic and/or heterocyclic.

USE - Used to **treat** or **prevent** diseases or conditions chosen from tissue damage resulting from cell damage or death due to necrosis or apoptosis, neuronal-mediated tissue damage or diseases, neural **tissue** damage resulting from **ischemia** and reperfusion injury, neurological disorders and neurodegenerative diseases, vascular stroke, cardiovascular disorders, age-related macular degeneration, AIDS and other immune senescence diseases, arthritis, atherosclerosis, cachexia, cancer, degenerative diseases of skeletal muscle involving replicative senescence, diabetes, head trauma, immune senescence, inflammatory bowel disorders, muscular dystrophy, osteoarthritis, osteoporosis, chronic pain, acute pain, neuropathic pain, nervous insult, peripheral nerve injury renal failure, retinal ischemia, septic shock and skin aging, diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or conditions induced or exacerbated by cellular senescence, to effect neuronal activity such as stimulation of damaged neurons (from cerebral ischemia and reperfusion injury), promotion of neuronal degeneration, **prevention** of neurodegeneration and to **treat** neurological disorders including those of peripheral neuropathy caused by physical injury or disease state, traumatic brain injury, physical damage to the spinal cord, stroke associated with brain damage, demyelinating disease and neurological disorder relating to neurodegeneration (Alzheimer's, Parkinson's or Huntington's disease, amyotrophic lateral sclerosis), to **treat** arthritis, diabetes, inflammatory bowel disorders (colitis, Crohn's

disease), cardiovascular disorders (coronary artery disease, myocardial infarction, angina pectoris, cardiogenic shock and cardiovascular tissue damage, septic shock (endotoxic shock), cancer (ACTH-producing tumors, acute lymphocytic or non-lymphocytic, chronic lymphocytic or myelocytic, or hairy-cell leukemia, adrenal cortical, bladder, brain, breast, cervix, colorectal, endometrial, esophageal, gallbladder, head and neck, kidney, liver, lung (small and/or non-small cell), ovarian, ovary (germ-cell), prostate, pancreatic, penile, skin, stomach, testicular, thyroid, uterine, vaginal or vulval cancer, cutaneous T-cell, Hodgkin's or non-Hodgkin's lymphoma, Ewing's, Kaposi's or soft-tissue sarcoma, malignant peritoneal or pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, osteosarcoma, retinoblastoma, sarcoma, squamous-cell carcinoma, trophoblastic neoplasm and Wilm's tumor), to radiosensitize tumor cells to extend or increase the lifespan or proliferative capacity of cells, and to alter the gene expression of senescent cells (all claimed). ACTIVITY - Neuroactive; anti-AIDS; antiarthritic; anti-atherosclerosis; anti-cancer; antidiabetic; gastrointestinal; analgesic; anti-ischemic; cardiovascular. MECHANISM OF ACTION - PARP inhibition.

ADVANTAGE - Have more potent and reliable effects with fewer side-effects than prior art. DESCRIPTION OF DRAWING(S) - Distribution of cross-sectional infarct area at representative levels along the rostrocaudal axis, as measured from the interaural line in non-**treated** animals and animals **treated** with 1-0 mg/kg of 3,4-dihydro-5-[1-(4-piperidinyl)-boxotyl]-1(2H)-isoquinoline. Dwg.1/2

L85 ANSWER 26 OF 93 MEDLINE DUPLICATE 4

1999415479 Document Number: 99415479. PubMed ID: 10487538. Inhibition of platelet-activating factor synthesis in human neutrophils and platelets by propionyl-L-carnitine. Triggiani M; Oriente A; Golino P; Gentile M; Battaglia C; Brevetti G; Marone G. (Division of Clinical Immunology, University of Naples Federico II, Italy.. triggian@unina.it) . BIOCHEMICAL PHARMACOLOGY, (1999 Oct 15) 58 (8) 1341-8. Journal code: 0101032. ISSN: 0006-2952. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Propionyl-L-carnitine (PrC) has been shown to exert beneficial effects in the **treatment** of myocardial and peripheral ischemia in man. These conditions are associated with the activation of circulating neutrophils and platelets. To determine whether PrC could affect the synthesis of lipid mediators known to influence neutrophil and platelet functions, we explored the effects of PrC on the synthesis of platelet-activating factor (PAF) and arachidonic acid (AA) **metabolites**. Preincubation (90 min) of human neutrophils with PrC (0.1-100 microM) inhibited the synthesis of PAF and of a PAF analog (1-alkyl-1'enyl-2-acetyl-sn-glycero-3-phosphoethanolamine: AEGPE) induced in vitro by the calcium ionophore A23187. In contrast, concentrations of PrC up to 100 microM did not influence the uptake of exogenous AA or the A23187-induced release of AA and eicosanoids from neutrophils in vitro. PrC (1 microM) also inhibited PAF synthesis from human platelets stimulated in vitro with thrombin, but had no effect on thrombin-induced aggregation. Oral administration of PrC (2 g/day for two weeks) to five normal volunteers resulted in a significant inhibition of PAF and AEGPE synthesis by neutrophils stimulated with A23187 ex vivo, with no effect on AA or eicosanoid release. These data indicate that PrC selectively inhibits in vitro and ex vivo PAF synthesis from human neutrophils and platelets without influencing AA metabolism or eicosanoid release. This effect of PrC might represent an additional mechanism by which this molecule can exert protective effects in **tissue ischemia** and in other inflammatory diseases associated with neutrophil and platelet activation.

Searched by: Mary Hale 308-4258 CM-1 1E01

L85 ANSWER 27 OF 93 MEDLINE DUPLICATE 5
1999247496 Document Number: 99247496. PubMed ID: 10232536. Pathogenesis and pharmacological strategies for mitigating secondary damage in acute spinal cord injury. Amar A P; Levy M L. (Department of Neurological Surgery, University of Southern California, Los Angeles, USA.) NEUROSURGERY, (1999 May) 44 (5) 1027-39; discussion 1039-40. Ref: 106. Journal code: 7802914. ISSN: 0148-396X. Pub. country: United States. Language: English.

AB OBJECTIVE: Experimental models and clinical observations of acute spinal cord injury (SCI) support the concepts of primary and secondary injury, in which the initial mechanical insult is succeeded by a series of deleterious events that promote progressive **tissue** damage and **ischemia**. Whereas the primary injury is fated by the circumstances of the trauma, the outcome of the secondary injury may be amenable to **therapeutic** modulation. This article reviews the pathogenetic determinants of these two phases of injury and summarizes the pharmacological manipulations that may restore neurological function after SCI. METHODS: Experimental models of SCI and their inherent limitations in simulating human SCI are surveyed. The pathogenesis of primary and secondary injury, as well as the theoretical bases of neurological recovery, are examined in detail. The effects of glucocorticoids, lazeroids, gangliosides, opiate antagonists, calcium channel blockers, glutamate receptor antagonists, antioxidants, free radical scavengers, and other pharmacological agents in both animal models and human trials are summarized. Practical limitations to inducing neural regeneration are also addressed. RESULTS: The molecular events that mediate the pathogenesis of SCI are logical targets for pharmacological manipulation and include glutamate accumulation, aberrant calcium fluxes, free radical formation, lipid peroxidation, and generation of arachidonic acid **metabolites**. Enhancement of neural regeneration and plasticity comprise other possible strategies. CONCLUSION: Pharmacological agents must be given within a narrow window of opportunity to be effective. Although many **therapeutic** agents show potential promise in animal models, only methylprednisolone has been shown in large, randomized, double-blinded human studies to enhance the functional recovery of neural elements after acute SCI. Future **therapy** is likely to involve various combinations of these agents.

L85 ANSWER 28 OF 93 MEDLINE DUPLICATE 6
2000058816 Document Number: 20058816. PubMed ID: 10593243. Enzymatic antioxidant defence mechanism in rat intestinal **tissue** is changed after **ischemia**-reperfusion. Effects of an allopurinol plus antioxidant combination. Kacmaz M; Ozturk H S; Karaayvaz M; Guven C; Durak I. (Department of Biochemistry, Ibn-I Hospital, Ankara, Turkey.) CANADIAN JOURNAL OF SURGERY, (1999 Dec) 42 (6) 427-31. Journal code: 0372715. ISSN: 0008-428X. Pub. country: Canada. Language: English.

AB OBJECTIVES: To establish the antioxidant status of rat intestinal **tissues** after **ischemia**-reperfusion and to determine if pretreatment with an allopurinol and antioxidant vitamin combination gives any protection against mucosal injury. EXPERIMENTAL ANIMALS: Twenty rats were divided into 4 groups of 5 animals each. METHODS: Group 1 (control) rats were not subjected to ischemia-reperfusion and received no allopurinol plus vitamin combination; group 2 rats received vitamins C (200 mg/kg) and E (100 mg/kg) and allopurinol (50 mg/kg) combination daily for 3 days preoperatively; group 3 rats were subjected to ischemia-reperfusion only; and group 4 rats were subjected to ischemia-reperfusion and received the vitamin and allopurinol combination. MAIN OUTCOME MEASURES: Activities of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) enzymes, the level of

thiobarbituric acid-reagent substances (TBARS) and histologic grading of tissue samples. RESULTS: SOD and GSH-Px activities were decreased, but the CAT activity and TBARS level increased. Pretreatment of the rats with the allopurinol-vitamin C-**vitamin E** combination did not have any significant effect on the enzyme activities. However, it resulted in important reductions in the TBARS tissue levels. Histologic investigation revealed significant mucosal injury in group 3 rats compared with group 4 rats (mean [and standard deviation] for grading, 4.6 [0.5] versus 1.8 [0.4]). CONCLUSIONS: The enzymatic antioxidant defence system was significantly changed after **ischemia**-reperfusion and intestinal **tissue** was exposed to increased oxidant stress, the results of which were peroxidation of some cellular structures and increased concentrations of oxidative products. Although antioxidant **treatment** did not drastically affect the enzyme activities or afford complete protection of cellular structures against deformation, it apparently could eliminate oxygen radicals and **prevent** peroxidative reactions.

L85 ANSWER 29 OF 93 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 7
1999:473429 Document No. 131:284590 The role of the myocardial sodium-hydrogen exchanger in mediating ischemic and reperfusion injury: from amiloride to cariporide. Karmazyn, Morris (Department of Pharmacology and Toxicology, University of Western Ontario, London, ON, N6A 5C1, Can.). Annals of the New York Academy of Sciences, 874(Heart in Stress), 326-334 (English) 1999. CODEN: ANYAA9. ISSN: 0077-8923. Publisher: New York Academy of Sciences.

AB A review, with 33 refs. There is convincing evidence that the Na-H exchanger (NHE) plays a pivotal role in mediating **tissue** injury during **ischemia** and reperfusion. Extensive studies with NHE inhibitors have consistently shown protective effects against ischemic and reperfusion injury in a large variety of exptl. models and animal species, particularly in terms of attenuating contractile dysfunction. These protective effects of NHE inhibition appear to be superior to other strategies, including ischemic preconditioning. Such studies have contributed greatly to the overwhelming evidence that NHE activation mediates ischemic and reperfusion injury. The NHE inhibitor HOE 642 (cariporide) is currently undergoing clin. evaluation in high-risk cardiac patients. Moreover, there is now emerging evidence that NHE may be involved in mediating cardiotoxicity directly produced by various ischemic **metabolites** such as lipid amphiphiles or reactive oxygen species. NHE inhibition also attenuates apoptosis in the ischemic myocardium, a process that may be of importance in the subsequent development of postinfarction heart failure. In conclusion, NHE represents an important adaptive process in response to intracellular acidosis that results in a paradoxical contribution to cardiac tissue injury.

L85 ANSWER 30 OF 93 MEDLINE
1999357029 Document Number: 99357029. PubMed ID: 10429960. Free radical scavengers to **prevent** reperfusion injury following experimental warm liver ischaemia. Is there a real physiological benefit?. Chavez-Cartaya R; Jamieson N V; Ramirez P; Marin J; Pino-Chavez G. (Department of Surgery, Addenbrookes Hospital, Cambridge, United Kingdom.) TRANSPLANT INTERNATIONAL, (1999) 12 (3) 213-21. Journal code: 8908516. ISSN: 0934-0874. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Free radical scavengers have been utilized to **prevent** the consequences of ischemia, however, results do not seem conclusive. In our study we analyzed the blood flow, function, and histology of rat liver **tissue** after warm liver **ischemia**, in order to assess the effect of free radicals in liver reperfusion injury. N-acetyl cysteine

(NAC), tocopherol, allopurinol, and superoxide dismutase (SOD), pharmacological agents expected to protect from injury mediated by free radicals, were investigated. Laser Doppler flowmetry and photometry were utilized to measure post-ischemic microcirculatory changes as an expression of ischemia-reperfusion injury in a model of segmental liver ischemia in the rat, with an ischemic time of 45 min. Galactose elimination capacity, ALT and histology were used to assess the functional and morphological consequences of ischemia after 24 h of reperfusion. The overall mean blood flow over 1 hour after reperfusion was of 33.9% (SD 11.2) of the normal, non-ischemic control. NAC (31.2% SD 10.9) did not show any protective effect and in some cases the effect seemed to be negative. Tocopherol (41.7% SD 5.1) marginally improved post ischemic liver tissue blood flow. **Treatment** with allopurinol did not show any beneficial effects (37.5% SD 14.2). Only animals **treated** with SOD showed an improvement of the post ischemic liver microcirculation (57.9% SD 14.4)($P < 0.001$) and function. Only SOD produced statistically significant differences in galactose elimination capacity, compared with those of the ischemic control group. This moderately protective effect of SOD is encouraging, however, the relevance of all these compounds in a broader pathophysiological setting remains unproven.

L85 ANSWER 31 OF 93 CAPLUS COPYRIGHT 2003 ACS
1999:504908 Document No. 131:349643 Nitric oxide in ischemia-reperfusion injury. Stewart, A. G.; Barker, J. E.; Hickey, M. J. (Bernard O'Brian Institute of Microsurgery, Victoria, 3065, Australia). Ischaemia-Reperfusion Injury, 180-195. Editor(s): Grace, Pierce A.; Mathie, Robert T. Blackwell: Oxford, UK. (English) 1999. CODEN: 67YVA2.
AB A review, with 118 refs. Topics discussed include: pathophysiol. of nitric oxide and its **metabolites**; organ-specific effects of nitric oxides and synthesis inhibitors in ischemia-reperfusion injury; and prospects for **therapeutic** application of nitric oxides donors and synthesis inhibitors in ischemia-reperfusion injury.

L85 ANSWER 32 OF 93 CAPLUS COPYRIGHT 2003 ACS
1999:318526 Document No. 131:98550 The role of transition metal ions in free radical-mediated damage. Chevion, Mordechai; Berenshtein, Eduard; Zhu, Ben-Zhan (Department of Cellular Biochemistry, Hebrew University-Hadassah Schools of Medicine and Dental Medicine, Jerusalem, 91120, Israel). Reactive Oxygen Species in Biological Systems: An Interdisciplinary Approach, 103-131. Editor(s): Gilbert, Daniel L.; Colton, Carol A. Kluwer Academic/Plenum Publishers: New York, N. Y. (English) 1999. CODEN: 67RAA6.
AB A review and discussion with many refs. on the site-specific mechanism of metal-mediated prodn. of free radicals, role of transition metal ions in converting low reactive mols. to highly reactive species, natural and xenobiotic mols. participating in site-specific damage, superoxide radical, ascorbate, pyrimidines, paraquat, peroxides, phenolic compds., hydrazines, thiols, involvement of iron and copper in **tissue** injury assocd. with **ischemia** and reperfusion, heart, brain, eye, intervention and **prevention**, Pull mechanism of protection, Push mechanism of protection, Pull-Push Mechanism of Protection, methods for the detection of redox-active labile pools of transition metals, the bleomycin assay for iron, the phenanthroline assay for copper, ESR/Ascorbate assay. ESR/DFO-nitric oxide assay, labile iron pool (LIP) assay, ascorbate DNA breakage and ascorbate-driven conversion of salicylate to its hydroxylated **metabolites**, and DFO-available LMWI.

L85 ANSWER 33 OF 93 MEDLINE
1998411462 Document Number: 98411462. PubMed ID: 9737936. Beneficial

Searched by: Mary Hale 308-4258 CM-1 1E01

effect of raxofelast, an hydrophilic **vitamin E** analogue, in the rat heart after ischemia and reperfusion injury. Campo G M; Squadrito F; Campo S; Altavilla D; Quartarone C; Ceccarelli S; Ferlito M; Avenoso A; Squadrito G; Saitta A; Caputi A P. (Institute of Pharmacology, School of Medicine, Messina, Italy.) JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY, (1998 Aug) 30 (8) 1493-503. Journal code: 0262322. ISSN: 0022-2828. Pub. country: ENGLAND: United.Kingdom. Language: English.

AB Several studies report that among the antioxidant agents used to reduce injury after myocardial ischemia/reperfusion, analogues of **vitamin E** (VE) seem to have a significant efficacy. Raxofelast is a potent antioxidant agent under investigation, structurally related to VE, having an excellent bioavailability and favourable physicochemical properties. We assessed raxofelast in a rat model of myocardial damage induced by 1 h of left coronary artery occlusion followed by 6 h of reperfusion. Myocardial **ischemia**/reperfusion produced: wide **tissue** necrosis (50.3+/-10.3%); membrane peroxidation, evaluated by assessing cardiac malondialdehyde (MAL) (87.8+/-15.8 nmol/g tissuev 9.53+/-2.4 nmol/g tissue) and plasma conjugated dienes (CD) (8.73+/-1.86 DeltaABS/mlv 1.61+/-0.45 DeltaABS/ml); endogenous antioxidant wasting [cardiac VE=23.5+/-10.2 nmol/g tissuev 61.4+/-13.4 nmol/g tissue, cardiac reduced glutatione (GSH)=2.15+/-1.23 micromol/g proteinv 7.34+/-0.92 micromol/g protein and cardiac superoxide dismutase (SOD)=8.9+/-4.1 U/mg proteinv 17. 5+/-4.2 U/mg protein]; depressed mean arterial blood pressure (MAP) (61.4+/-5.8 mmHgv 85.3+/-6.2 mmHg); heart rate (HR) (275+/-35 beats/minv 368+/-34 beats/min) and left-ventricular derivative developed force (LV dP/dtmax) (1050+/-187 mmHg/sv 2520+/-194 mmHg/s); and cardiac neutrophil accumulation, evaluated by assessing cardiac myeloperoxidase (MPO) (9.23+/-2.1 U/g tissuev 0.92+/-0.12 U/g tissue). Administration of raxofelast (25, 50 and 100 mg/kg i.p. 5 min after occlusion) limited myocardial necrosis (22.3+/-14.8%P<0. 005, following the highest dose), reduced lipid peroxidation (MAL=43. 5+/-14.7 nmol/g tissueP<0.001 and CD=4.01+/-2.21 DeltaABS/mlP<0.001, following the highest dose), restored the endogenous antioxidants VE (52.8+/-14.2 nmol/g tissueP<0.001, following the highest dose), SOD (14.2+/-2.7 U/mg proteinP<0.001, following the highest dose) and GSH (4.92+/-1.33 micromol/g proteinP<0.005, following the highest dose), improved hemodynamic parameters (MAP=68.1+/-5.3 mmHgP<0.05, HR=317+/-27 beats/minP<0.05, LV dP/dtmax=1427+/-143 mmHg/sP<0.05, following the highest dose) and reduced myocardial neutrophil infiltration (MPO=5..1+/-1.5 U/g tissueP<0.001, following the highest dose). These data suggest that raxofelast could be considered a useful drug to reduce myocardial infarction.

L85 ANSWER 34 OF 93 MEDLINE DUPLICATE 8

1998366814 Document Number: 98366814. PubMed ID: 9703254. Ferrous ion diminished the antiarrhythmic effect of naloxone in myocardial ischemia of isolated rat hearts. Kuo J S; Wu J P; Tsai P J; Yang C S. (Department of Education and Research, Taichung Veterans General Hospital, Taiwan, ROC.) BIOLOGICAL AND PHARMACEUTICAL BULLETIN, (1998 Jul) 21 (7) 710-2. Journal code: 9311984. ISSN: 0918-6158. Pub. country: Japan. Language: English.

AB This investigation was to examine the effect of ferrous ion (a prooxidant) on the antiarrhythmic effect of naloxone (an endogenous opioid receptor antagonist) in isolated rat hearts. Isolated Sprague-Dawley rat hearts were perfused in the Langendorff mode and myocardial ischemia was performed by ligating the left descending coronary artery. Cardiac rhythm was recorded. Heart alpha-tocopherol concentrations were analyzed. Naloxone (1.2 micromol/heart) was effective in reducing the severity of arrhythmia (arrhythmia score; mean+/-S.E.M: 2.82+/-0.69 for naloxone vs. 5.18+/-0.38 for control, p<0.01). Fe2+ (100 nmol/heart) alone did not

significantly affect the arrhythmia score (5.63+/-0.32) when compared with the control, however, Fe2+ administration did cause significant early onset of ventricular premature contraction and ventricular tachycardia. Additionally, Fe2+ administration diminished the naloxone's antiarrhythmic effect (arrhythmia score 4.12+/-0.40). Alpha-tocopherol, a major free radical scavenger that exerts protective functions on heart **tissues** during myocardial **ischemia**/reperfusion, was significantly higher in the naloxone-**treated** group (59.05+/-3.00 nmol/g wet wt) than in the control group (43.84+/-4.17 nmol/g wet wt, $p<0.05$). These results suggest that endogenous opioid peptides and reactive oxygen species might be related to ischemia-induced arrhythmia.

L85 ANSWER 35 OF 93 MEDLINE DUPLICATE 9

1998324000 Document Number: 98324000. PubMed ID: 9659815. The myocardial sodium-hydrogen exchanger (NHE) and its role in mediating ischemic and reperfusion injury. Karmazyn M. (Department of Pharmacology and Toxicology, University of Western Ontario, London, Canada.. mkarm@julian.uwo.ca) . KEIO JOURNAL OF MEDICINE, (1998 Jun) 47 (2) 65-72. Ref: 56. Journal code: 0376354. ISSN: 0022-9717. Pub. country: Japan. Language: English.

AB A major mechanism by which the heart adapts to intracellular acidosis during ischemia and recovers from the acidosis after reperfusion is through the sodium-hydrogen exchanger (NHE). There are at least 5 NHE isoforms thus-far identified with the NHE-1 subtype representing the major one found in the mammalian myocardium. This 110 kDa glycoprotein extrudes protons concomitantly with Na influx in a 1:1 stoichiometric relationship rendering the process electroneutral. Although NHE is critical for the maintenance of intracellular pH during acid loading conditions such as ischemia, there is convincing evidence that it also plays a pivotal role in mediating **tissue** injury during **ischemia** and reperfusion. The mechanism for this paradoxical deleterious role of NHE reflects the fact that under conditions of **tissue** stress, including **ischemia**, Na-K adenosine triphosphate (ATP)ase is inhibited thereby limiting Na extrusion resulting in an elevation in intracellular Na concentrations. The latter effect, in turn, will increase intracellular Ca concentrations via Na-Ca exchange. In addition, NHE-1 expression in the diseased myocardium is increased suggesting that elevated production of the antiporter represents a long-term adaptive process in an attempt by the cardiac cell to regulate intracellular pH which, paradoxically, contributes to cardiac pathology. Extensive studies using NHE inhibitors such as amiloride or its analogs, or more specific compounds including 3-methylsulphonyl-4-piperidinoloenzoyl-guanidine methanesulphonate (HOE 694) or 4-isopropyl-3-methylsulphonylbenzcyl-guanidine methane sulphonate (HOE 642) have consistently shown protective effects against ischemic and reperfusion injury in a large variety of experimental models and animal species particularly in terms of attenuating contractile dysfunction. Such studies have contributed greatly to the overwhelming evidence that NHE activation mediates ischemic and reperfusion injury. Indeed, HOE 642 (Cariporide) is currently undergoing clinical evaluation in high risk cardiac patients. Moreover, there is now emerging evidence that NHE may be involved in mediating cardiotoxicity directly produced by various ischemic **metabolites** such as lipid amphiphiles or reactive oxygen species. In this regard, we have demonstrated that NHE inhibitors can effectively attenuate the cardiac injury produced by lysophosphatidylcholine and hydrogen peroxide. In addition, it now appears that NHE inhibition reduces apoptosis in the ischemic myocardium, a process which may be of importance in the subsequent development of postinfarction heart failure. In conclusion, NHE represents an important adaptive process in response to intracellular acidosis resulting in a paradoxical contribution to cardiac tissue injury.

Searched by: Mary Hale 308-4258 CM-1 1E01

L85 ANSWER 36 OF 93 MEDLINE DUPLICATE 10
1998288375 Document Number: 98288375. PubMed ID: 9533827. Effects of perfluorooctylbromide and **vitamin E** on **ischemia** induced retinal oxidative **tissue** damage.
Augustin A J; Spitznas M; Koch F; Grus F; Lutz J. (Department of Ophthalmology, University of Bonn, Sigmund-Freud-Strasse 25, Bonn, 53105, Germany.) EXPERIMENTAL EYE RESEARCH, (1998 Jan) 66 (1) 19-24. Journal code: 0370707. ISSN: 0014-4835. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The aim of this study was to investigate the extent to which ischemia and reperfusion lead to oxidative damage of the retinal tissue and investigate how ischemic and reperfused retinal tissues react to the application of perfluorooctylbromide (PFOB) and, if this reaction can be influenced by protective drugs such as **vitamin E** (Vit.E). The experiments were performed with 60 male Wistar rats, divided into 12 groups using an established model of reversible ischemia and reperfusion of the globe. Grouping of animals was carried out according to different ischemia and reperfusion periods and different **therapeutic** regimens (PFOB, Vit.E). **Treatment** with PFOB and/or Vit.E was performed after 60 min of ischemia with 60 min of reperfusion. At the end of the experiments thiobarbituric acid reactive substances (TBARS) were determined in the retinal tissues and served as parameters of oxidative tissue damage. Ischemia of up to 60 min led to a significant increase in TBARS values. Ninety and 120 min of ischemia led to no further significant elevation compared to the 60 min or 90 min group. Following 60 min of ischemia, a reperfusion period of 15 min led to an increase in TBARS values that was significant ($P<0.05$) after 30 and 60 min. Addition of PFOB resulted in a further significant ($P<0.05$) increase in TBARS values as compared to the respective group without **treatment**. Vit. E alone did not change the values significantly compared to the respective group without **treatment**. However, the application of Vit.E in addition to PFOB led to a significant reduction in TBARS values. Ischemia resulted in severe oxidative retinal tissue damage, which increased during reperfusion. The reperfusion damage might be due to the known depletion of protecting substances such as **vitamin E**. Enhancement of oxygen supply by PFOB during reperfusion without any tissue protection leads to more severe damage. Thus, additional protection of the tissue by powerful antioxidants is necessary when providing oxygen for better tissue recovery.

L85 ANSWER 37 OF 93 MEDLINE DUPLICATE 11
97303304 Document Number: 97303304. PubMed ID: 9159629. Effect of preoperative supplementation with alpha-tocopherol and ascorbic acid on myocardial injury in patients undergoing cardiac operations. Westhuyzen J; Cochrane A D; Tesar P J; Mau T; Cross D B; Frenneaux M P; Khafagi F A; Fleming S J. (Department of Cardiology, Royal Brisbane Hospital, Australia.) JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (1997 May) 113 (5) 942-8. Journal code: 0376343. ISSN: 0022-5223. Pub. country: United States. Language: English.

AB Augmentation of antioxidant defenses may help protect **tissues** against **ischemia**-reperfusion injury associated with operations involving cardiopulmonary bypass. In this study we examined the effect of pretreating patients with alpha-tocopherol (**vitamin E**) and ascorbic acid (vitamin C) or placebo on injury to the myocardium. Seventy-six subjects undergoing elective coronary artery bypass grafting participated in a prospective, double-blind, placebo-controlled randomized trial, receiving either placebo or both 750 IU dl-alpha-tocopherol per day for 7 to 10 days and 1 gm ascorbic acid 12 hours before the operation.

Searched by: Mary Hale 308-4258 CM-1 1E01